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PART 1. TOTAL SYNTHESIS OF (-)-KHUSIMONE, (+)-ZIZANOIC ACID AND (-)-EPIZIZANOIC ACID

PART 2. SYNTHETIC STUDIES ON CEDRENOID SESQUITERPENES

by

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A THESIS

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OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

PART 1. TOTAL SYNTHESIS OF (-)-KHUSIMONE, (+)-ZIZANOIC ACID AND (-)-EPIZIZANOIC ACID

PART 2. SYNTHETIC STUDIES ON CEDRENOID SESQUITERPENES

TO MY PARENTS AND SISTERS

ABSTRACT

The first part of this thesis describes a total synthesis of three zizaene sesquiterpenes, (-)-khusimone (I), (-)-epizizanoic acid (II) and (+)-zizanoic acid (III), starting from the commercially available (-)-ℓ-10-camphorsulfonic acid ammonium salt (IV).

Fusion of the salt IV with solid potassium hydroxide gave (-)-α-campholenic acid (V) which was converted to the corresponding methyl ester VI with methyl iodide and potassium carbonate in refluxing acetone. Ozonolysis of ester VI followed by reductive work-up using triphenylphosphine afforded keto aldehyde VII. Its cyclization to enone VIII was effected by p-toluenesulfonic acid in refluxing benzene. Irradiation of enone VIII with 1,1-diethoxyethene followed by hydrolysis of the photoadduct IX gave rise to a mixture of diketones X and XI in a ratio of 5:8. The latter product was converted to the former one by treatment with pyridinium bromide perbromide in acetic acid followed by reduction of the resulting enediones XII with zinc in acetic acid.

Selective ketalization of diketone X using 2-ethyl-2-methyl-1,3-dioxolane and p-toluenesulfonic acid gave rise to ketal XIII which was hydrolyzed to the corresponding acid XIV with alkali. Treatment of the sodium salt derived from acid XIV and sodium hydride with methyl magnesium bromide followed by esterification of the resulting hydroxy acid XV with diazomethane afforded alcohol XVI. On treatment with thionyl chloride in pyridine in

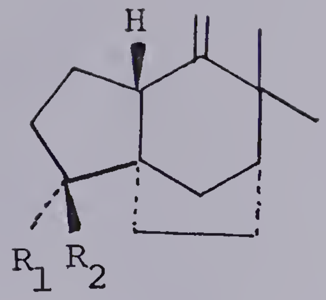
benzene, alcohol XVI underwent dehydration to give ester XVII which was subsequently reduced by lithium aluminium hydride to alcohol XVIII. Its conversion to the corresponding chloride XIX was effected by phosphorus oxychloride in pyridine. Hydrolysis of chloride XIX with hydrochloric acid and ring expansion of the product XX with ethyl diazoacetate and boron trifluoride etherate gave rise to keto ester XXI. When heated at reflux with sodium hydroxide in ethanol and water, keto ester XXI underwent concomitant decarbethoxylation and cyclization to give (-)-khusimone (I).

On treatment with dimethyl sulfonium methylide ylide, (-)-khusimone (I) was transformed to epoxide XXII. Boron trifluoride catalyzed rearrangement of epoxide XXII afforded aldehyde XXIII which was subsequently oxidized with Jones reagent to give (-)-epizizanoic acid (II). Alternatively, epimerization of aldehyde XXIII to XXIV followed by Jones oxidation resulted in the formation of (+)-zizanoic acid (III).

In the second part of this thesis, the preparation of trione XXV, a potential synthetic precursor of cedrenoid sesquiterpenes, is described. (-)-α-Campholenic acid (V) was first converted to ketone XXVI by treatment with methyllithium. Photooxidation of ketone XXVI followed by reductive work-up with triethyl phosphite gave rise to epimeric alcohols XXVII which were subsequently oxidized with active manganese dioxide to give enone XXVIII. Addition of 1-nitropropane to enone XXVIII was effected by using potassium carbonate as a base. The salt derived from the product XXIX

and one equivalent of sodium methoxide in methanol was subjected to ozonolysis. Reductive work-up using dimethyl sulfide afforded trione XXV.

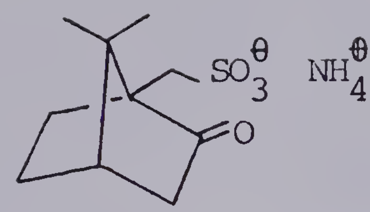
Results obtained from the preliminary studies on the transformation of trione XXV to cedrenoid sesquiterpenes are also discussed.



I $R_1, R_2 = O$

II $R_1 = COOH$; $R_2 = H$

III $R_1 = H$; $R_2 = COOH$



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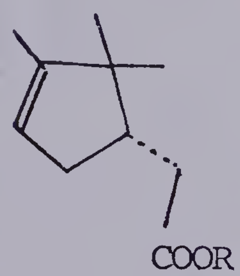
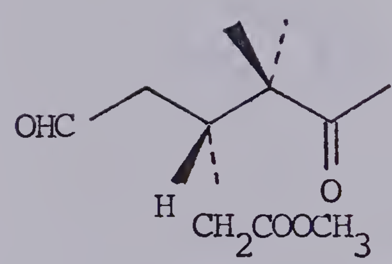


V $R = H$

VI $R = CH_3$



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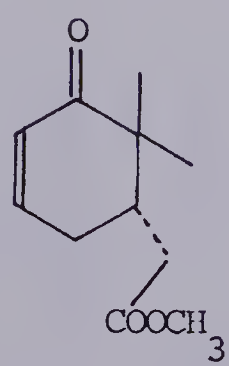

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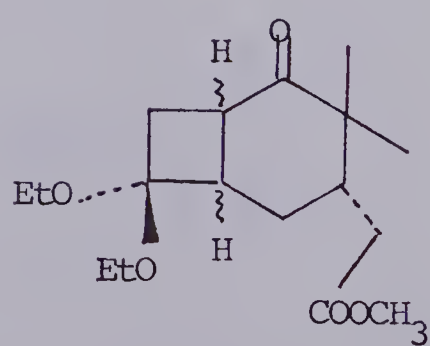

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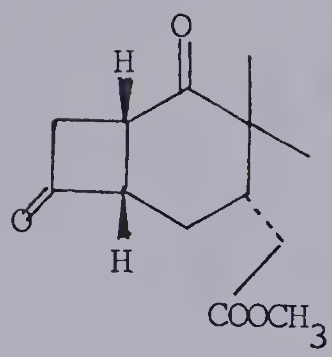

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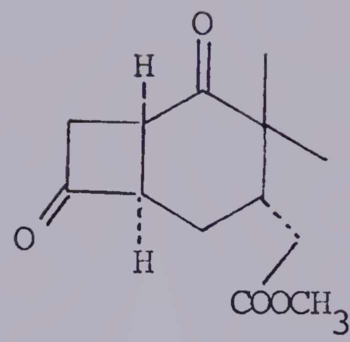

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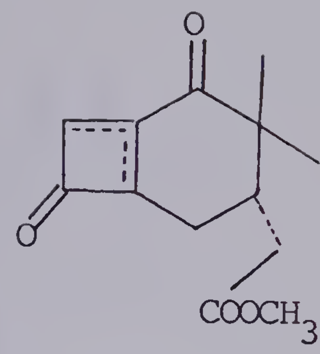

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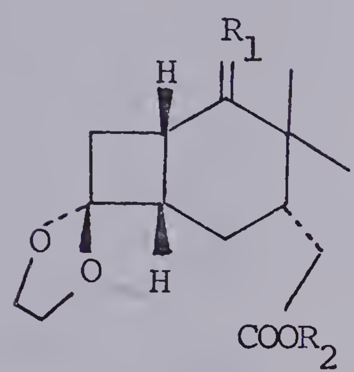
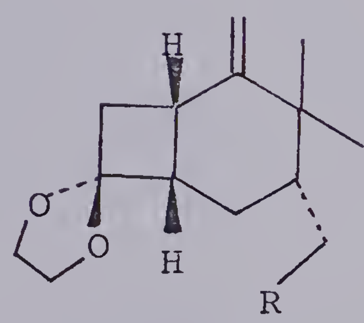


XIII $R_1 = O$; $R_2 = CH_3$

XIV $R_1 = O$; $R_2 = H$

XV $R_1 = OH, CH_3$; $R_2 = H$

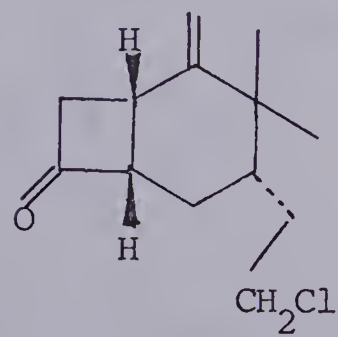
XVI $R_1 = OH, CH_3$; $R_2 = CH_3$



XVII $R = COOCH_3$

XVIII $R = CH_2OH$

XIX $R = CH_2Cl$



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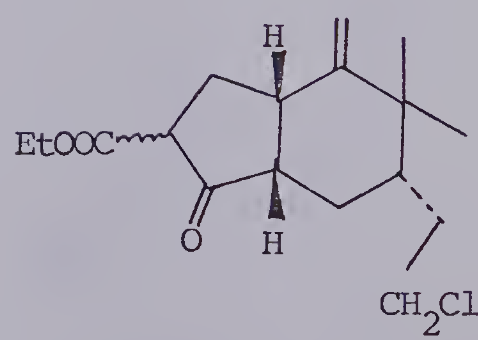

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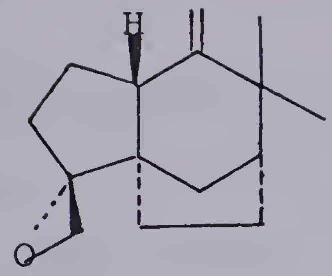

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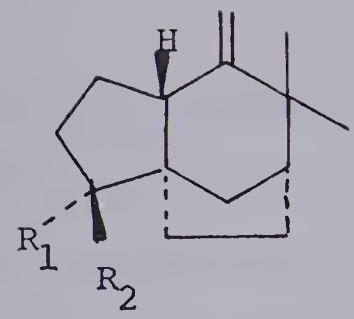
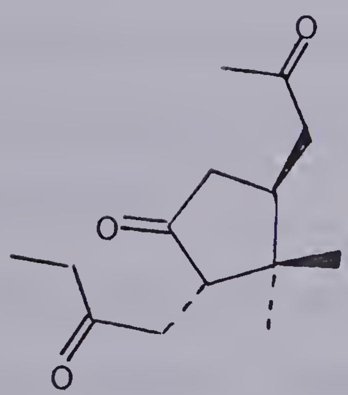


XXIII R_1 = CHO ; R_2 = H

XXIV R_1 = H ; R_2 = CHO



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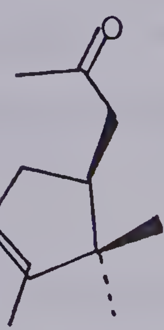

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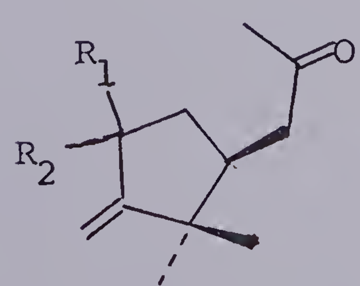
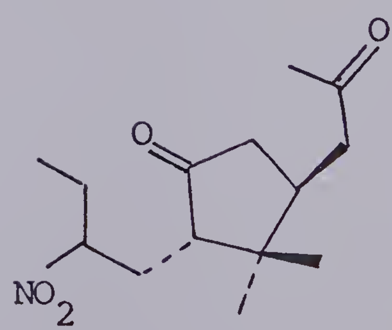


XXVII R_1 = OH ; R_2 = H

XXVIII R_1 , R_2 = O



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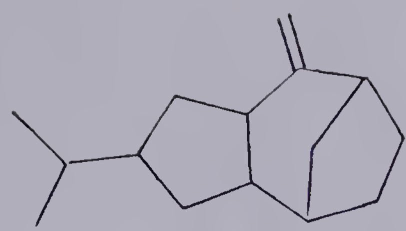
INTRODUCTION

The history of zizaene-type sesquiterpenes began about two decades ago when Chiurdoglu and Tullen isolated, from the essential oil of the vetiver indigenous to the Belgian Congo, three closely related sesquiterpenes, tricyclovetivene (1), bicyclovetivenol and tricyclovetivenol (2) to which they assigned structures 1-3 respectively. Four years later, Romanuk and Herout isolated a hydrocarbon, $C_{15}H_{24}$, from the oil of a Javanese vetiver (3). The infrared spectrum of this substance and its physical constants were in good agreement with those of the tricyclovetivene isolated by the Belgian workers. In 1966, Chakravarti and coworkers found a new sesquiterpene (4), named as khusimol, in the extracts from a South Indian vetiver. On the basis of the available information, they suggested two possible structures 4a or 4b for this naturally occurring alcohol. In the following year, Morikawa and Hirose (5) reported the isolation of the same alcohol from the essential oil of *Vetiveria zizaniodes* and postulated an additional alternative structure, 4c, for this compound. In examining the acidic constituents of the same essential oil, Yoshikoshi *et al*. (6) isolated a sesquiterpene carboxylic acid, zizanoic acid, which was shown to possess the identical carbon skeleton to that of khusimol by a chemical correlation via the common degradation product 5. These investigators also showed that the structures 4a and 4b previously assigned to khusimol were incorrect in as much as, the deuteration of ketone 5 resulted in the incorporat-



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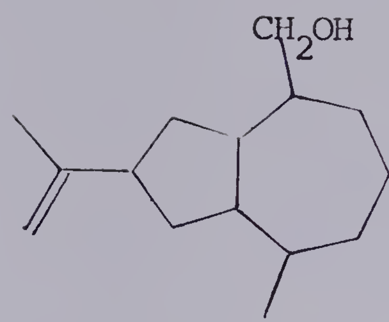

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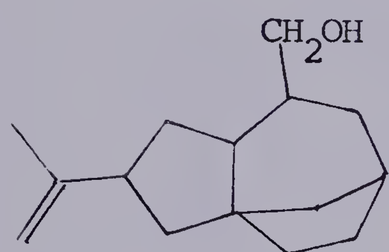

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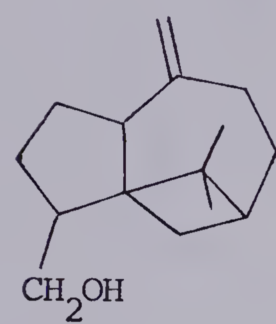
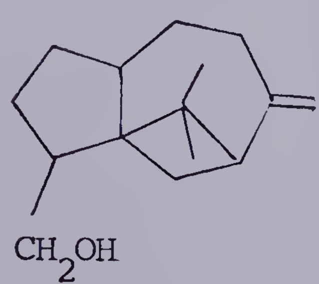
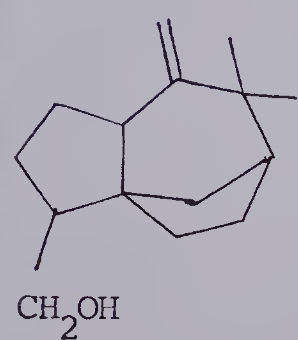


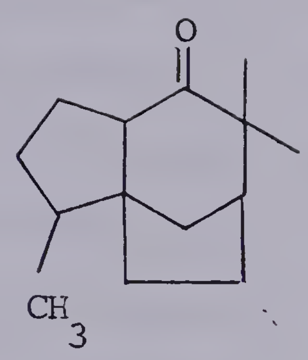
4a



4b



4c



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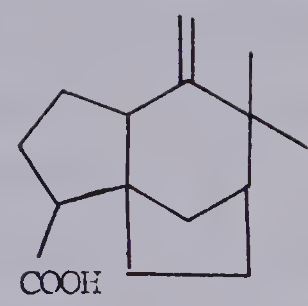

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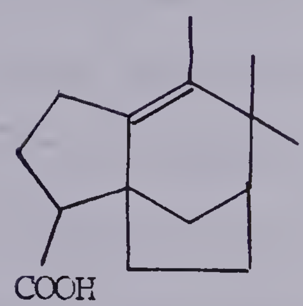

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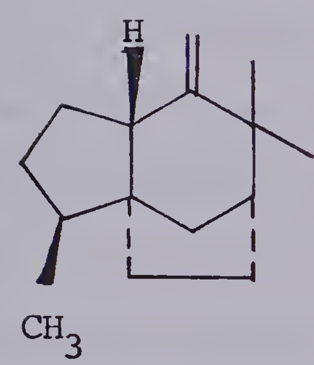

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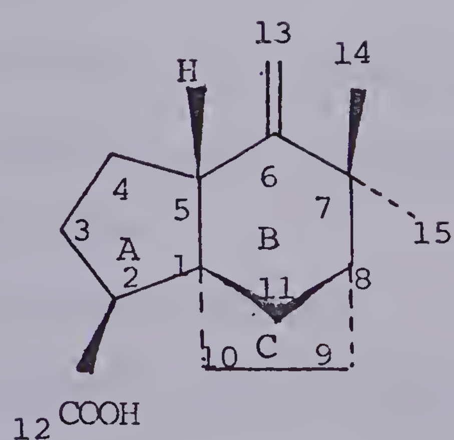

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ion of a single deuterium atom indicating the presence of one enolizable hydrogen alpha to the carbonyl. Based on this observation and other chemical evidence, as well as spectroscopic analyses, they concluded that the gross structure of zizanoic acid was as depicted in formula 6 and that that of khusimol was 4c. During the same period, the isolation of khusenic acid, khusenol and isokhusenic acid (7) from the oil of an Angolan vetiver was described by Nigam and coworkers (7-10). The two former compounds were later found to be identical with zizanoic acid and khusimol respectively and the equivalence of khusimol and tricyclovetivenol was also noted (9). Sakuma and Yoshikoshi (11) also obtained pure tricyclovetivene from vetiver oil and re-examined its structure. The nmr spectrum of this hydrocarbon was found to be incompatible with the structure 1 previously proposed by Chiurdoglu and Decot (1). In addition to two tertiary methyl groups and an exocyclic methylene group, the nmr spectrum displayed a doublet characteristic of a secondary methyl group. By further correlation with zizanoic acid, the structure of tricyclovetivene was revised to 8 (11)[1,2].

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[1]In several cases, different names were provided for the same natural product by independent research groups. To clarify the situation, these cases are summarized below.

khusenol = tricyclovetivenol = khusimol

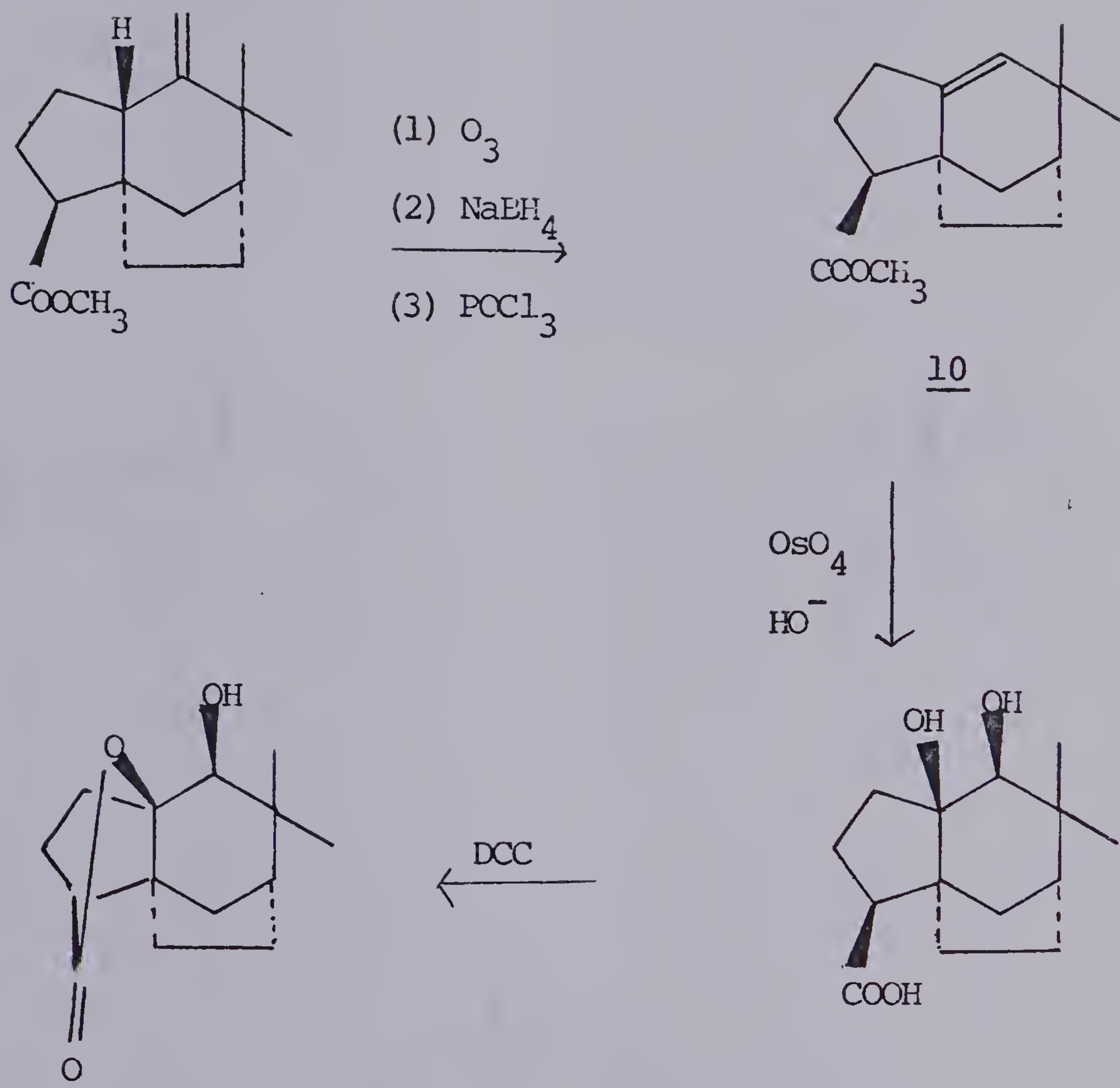
tricyclovetivene = khusene = zizaene = khusinene

zizanoic acid = khsenic acid

[2]Its stereochemistry follows from that of zizanoic acid (9) (*vide infra*)

In order to determine the stereochemistry of the zizaene-type compounds, ORD data of several derivatives of natural zizanoic acid were analysed (12). Application of octant rule and Cotton effect with the assistance of suitable model compounds of known absolute configuration suggested that the absolute stereochemistry of the three chiral centers (C-1, C-5 and C-8) of zizanoic acid was as depicted in formula 9. The configuration of the remaining chiral carbon bearing the carboxyl group was established as follows. According to the reaction sequence shown in Scheme 1, zizanoic acid was converted to the γ-lactone 12. Since the oxidation of ester 10 to diol 11 is expected to occur preferentially from the less hindered convex face of the molecule, the subsequent lactone ring formation requires a β-orientation of the carboxyl group. The complete structural assignment of zizanoic acid (9) was confirmed when khusimol was shown to possess absolute configuration indicated in formula 13 by an X-ray crystallographic analysis of its p-bromobenzoyl derivative (13).

In recent years, several additional members of the zizaene family have been obtained from natural sources. On further investigation of the vetiver oil , Yoshikoshi et al. isolated epizizanoic acid (14) (14), a minor acidic constituent, and zizanol (15) (15), a new sesquiterpene alcohol which was simultaneously obtained by Andersen (16) from Haitian and Reunionese varieties. The former compound was readily deduced to be the C-5 epimer of zizanoic acid (9) by isomerization of the corresponding methyl esters. The dehydroxylation product of zizanol (15) was found to be identical to zizaene (8) thus confirming its carbon



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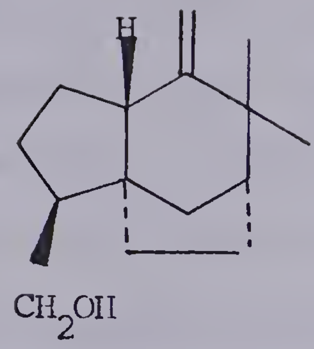
Scheme 1



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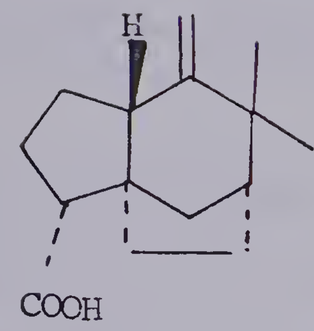

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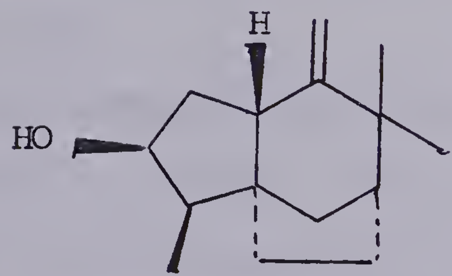

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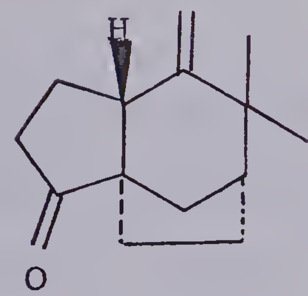

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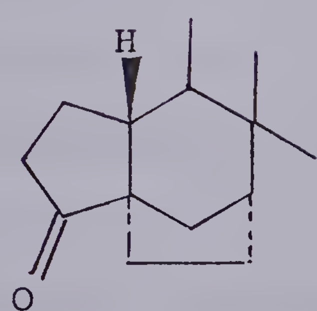

17

skeleton. The location and the orientation of the hydroxyl group was established by oxidation to the corresponding ketone which underwent epimerization at C-5 upon base treatment and upon hydride reduction gave predominantly zizanol (15).

Khusimone (16), a highly odoriferous ketone, is the simplest known member of the zizaene family. This norsesquiterpene was first isolated from Vetiveria zizaniodes by Chakravarti et al. (17) who also identified its structure by the correlation of its dihydro-derivative 17 with that prepared from khusimol (13). Minor quantities of khusimone (16) were later found in the extracts of Vetiveria bourbon (18).

The biosynthesis of zizaene sesquiterpenes has been a controversial topic (6,9,19-21). Two distinctly different pathways have been proposed for the production of these tricyclic compounds in nature. In view of the co-occurrence of zizaene (8), zizanoic acid (9) and khusimol (13) with α-vetivone (18) and β-vetivone (19)[2a], Ramage et al. (19) postulated a common biogenetic route for the formation of spiro-vetivene sesquiterpenes and those of the tricyclic zizaene-type involving the intermediacy of hinesol (20) as shown in Scheme 2. The feasibility of the key rearrangement 21→22 occurring in vivo was supported by the observation that solvolysis of the mesylate 23 in refluxing pyridine/triethylamine gave rise to the ketone 24 (22).

Another proposal (6,9,20-21) involves a pathway (Scheme 3) analogous to the cedrene biogenesis. Since both the relative and absolute stereochemistry of zizaene (8) are different from those of

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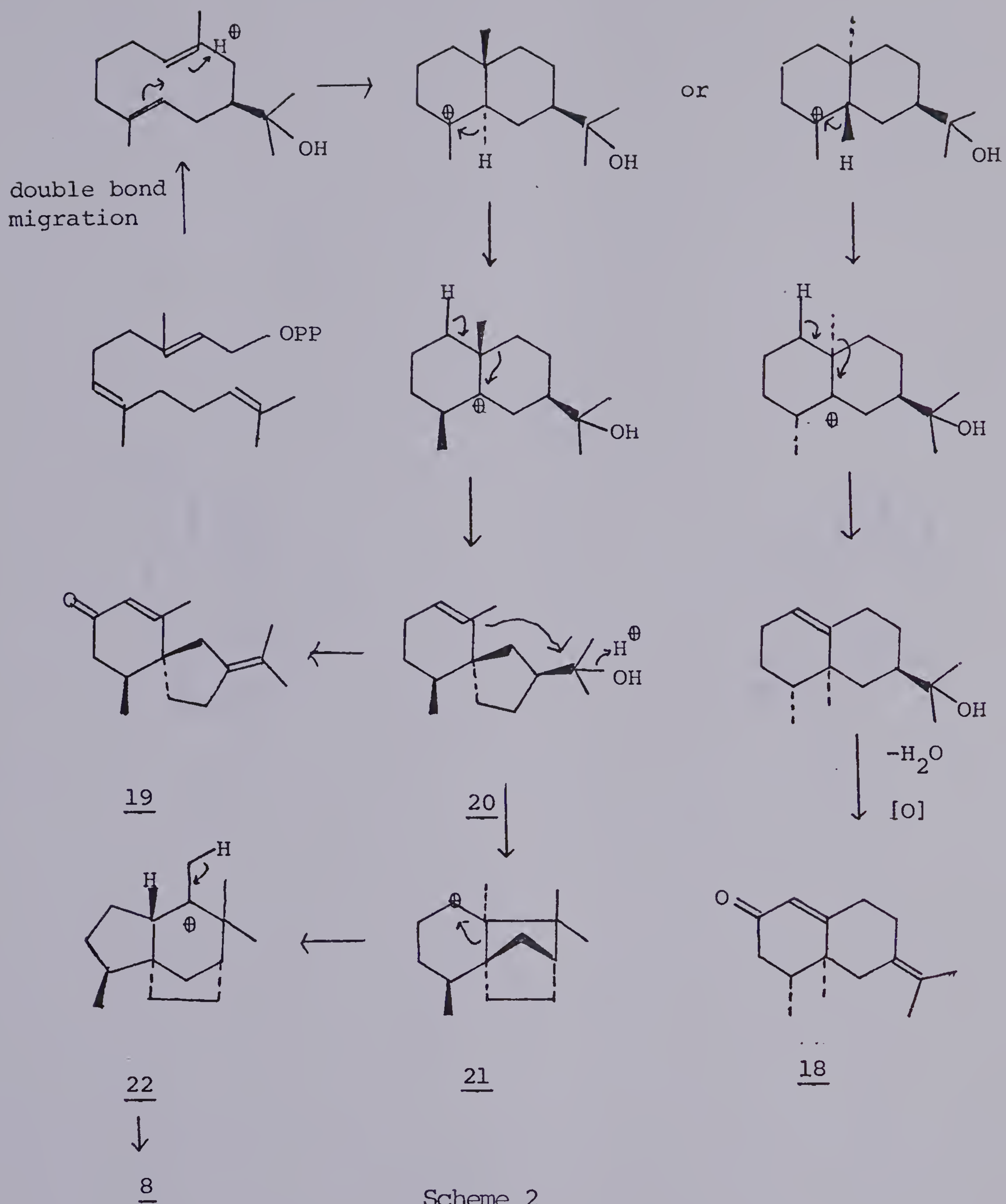
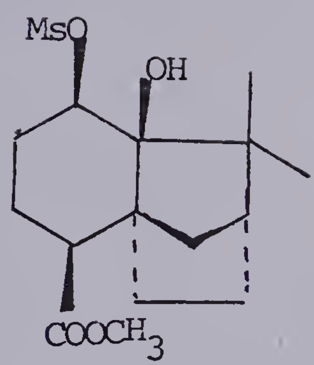
[2a]Natural β-vetivone was later shown to be the antipode of 19 (23).



Scheme 2



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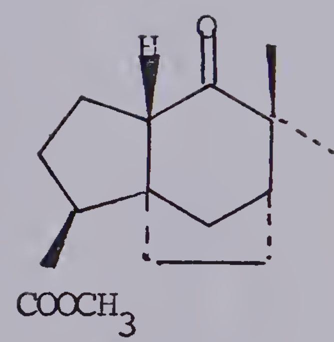

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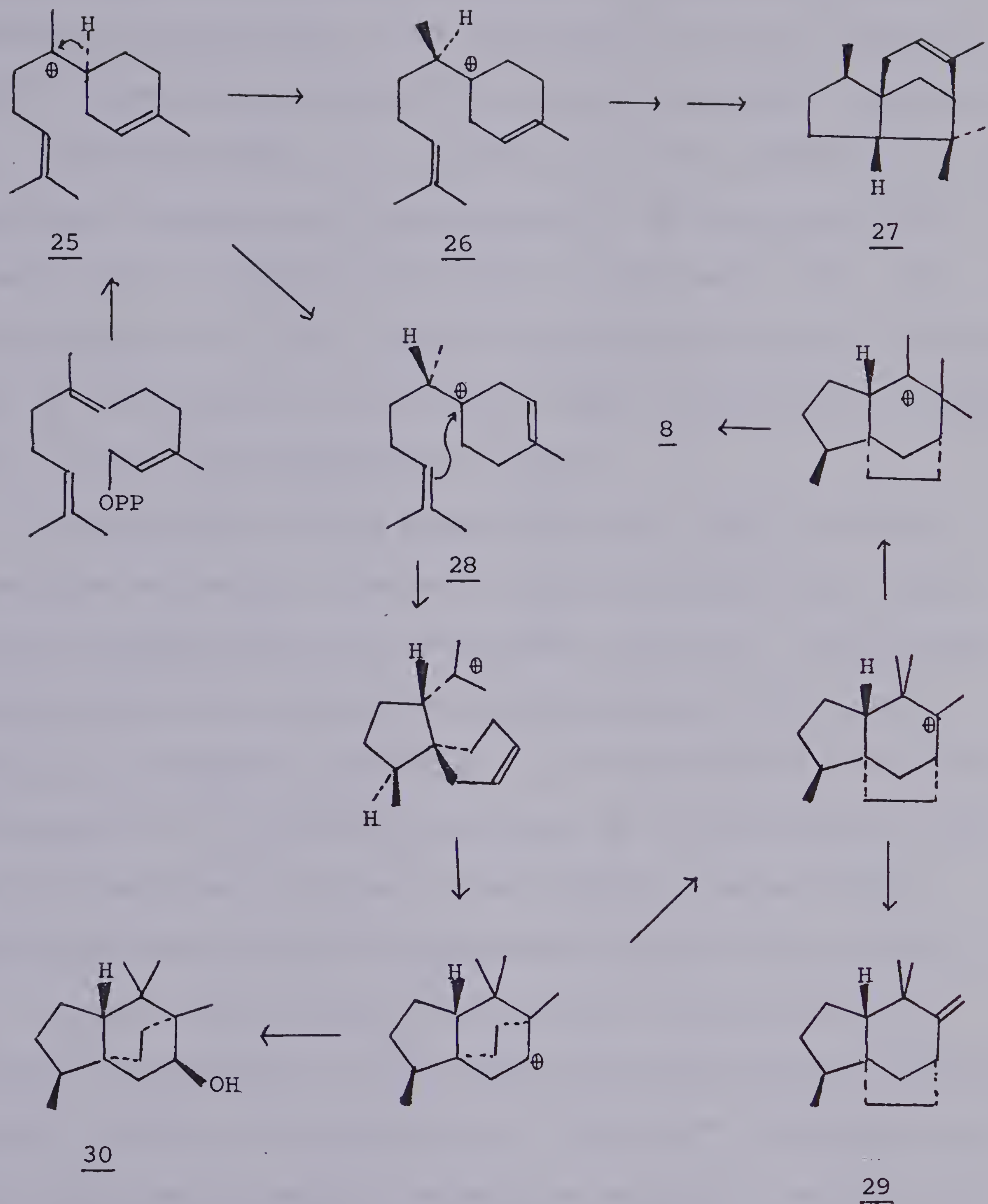


Scheme 3

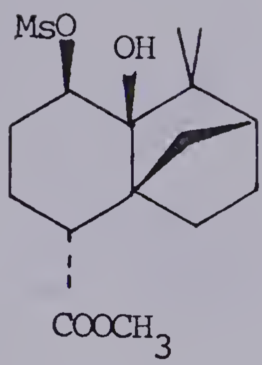
cedrene (27), the enantiomeric β-bisabolyl cations 26 and 28 are required as intermediates. It is interesting to note that these two bisabolyl ions may be generated from the same α-bisabolyl precursor 25 by 1,2-hydride shift to the opposite face of the carbonium ion. The postulated biogenetic route was supported by the isolation of prezizaene (29) (23) and allocedrol (30) (24) from vetiver oil. The rearrangement at the later stage of biogenesis has also been substantiated by the observation that prezizaene (29) is convertible to zizaene (8) in formic acid-tetrahydrofuran (23,25).

During the past several years, zizaene (8) and its cogeners have drawn considerable attention to their preparation and a number of total syntheses have been accomplished (22,26-30). The following features which are common to the natural products of the zizaene family are synthetically demanding: (a) the construction of the parent tricyclo[$6.2.1.0^{1,5}$]undecane ring system, (b) the installation of an exocyclic methylene unit, and (c) the control of stereochemistry, particularly the less stable trans-fused hydroindane ring junction.

In most of the existing total syntheses, the basic tricyclic skeleton was assembled with high efficiency using different approaches. In their synthesis of epizizanoic acid (14) (26,27), Yoshikoshi et al. effectively used a pinacolic rearrangement whereby the mesylate 31, prepared from (+)-methyl camphenecarboxylate (32) in fifteen steps, was converted to ketone 33 possessing the required ring system. A similar approach was independently employed by Ramage and coworkers (22). In connection with their synthetic studies on diterpene alkaloids, Wiesner and his collaborators developed an efficient

procedure for the preparation of bicyclo[3.2.1]octane derivatives (31). This method has been extended to their synthesis of zizaene (8) (28). Thus, as the key step, acetal 34 derived from phenol 35 in eight steps was treated with acetic acid to give ketol 36 as a result of concomitant deketalization and ring closure. The other total synthesis of zizaene (8) was reported by Coates and Sowerly (29) who utilized an intramolecular diazoalkane-carbonyl ring expansion reaction (32) and obtained an epimeric mixture of ketones 37 from the diazo compound 38. More recently, Büchi et al. (30) described an approach in which enone 39 was rearranged by p-toluenesulfonic acid to ketone 40, a process analogous to the later stage of a biogenetic proposal (vide supra). The ketone 40 was subsequently subjected to photooxidation and the resulting alcohol 41 was reduced with zinc and hydrogen chloride to give khusimone (16) and its C-5 epimer.

With the exception of Büchi's synthesis, all existing approaches to naturally occurring zizaene sesquiterpenes involve a compound of type 42 as an intermediate and utilize its ketone function to control the ring junction stereochemistry as well as to introduce an exo-methylene group. Such a synthetic strategy suffers from two major drawbacks. Firstly, the epimerization of the A/B ring junction from a cis-fusion to the desired trans one could not be achieved with high degree of efficiency due to the greater stability of the former arrangement, regardless of the type and the orientation of the C-2 substituent. For example, in the case of ketone 43, base-catalyzed epimerization gave an equilibrium mixture of which the desired trans-epimer



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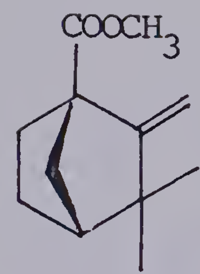

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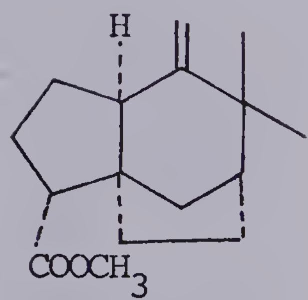

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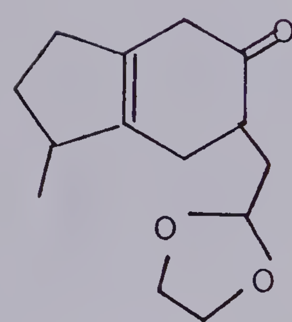

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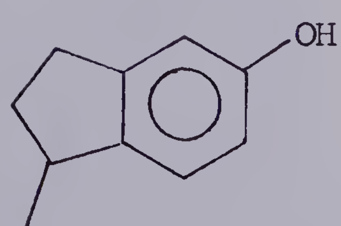

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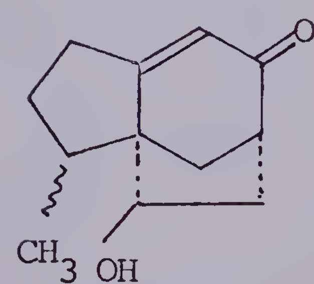

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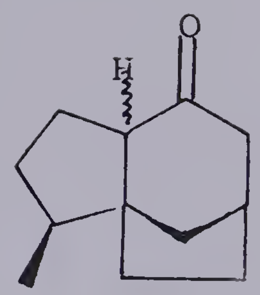

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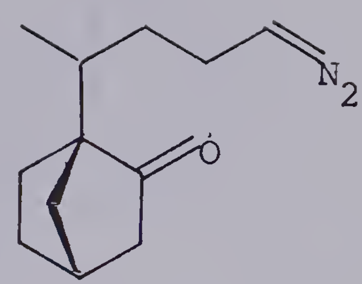

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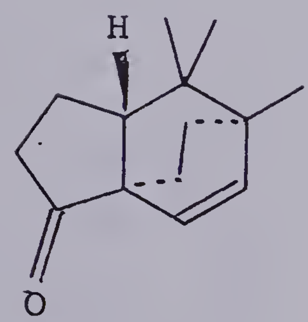

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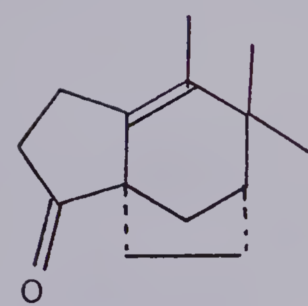

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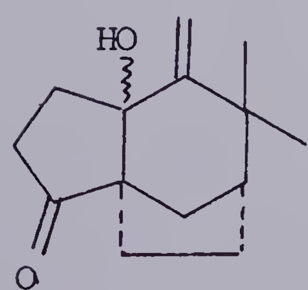

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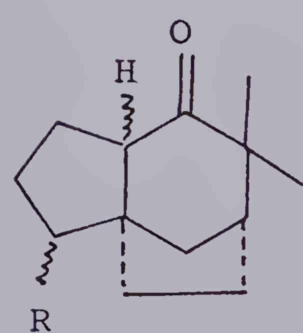

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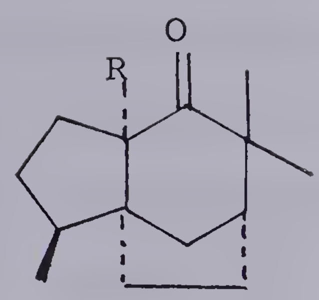
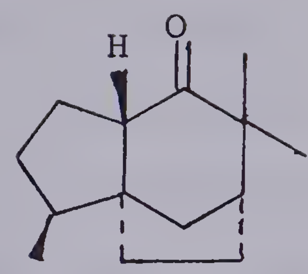


43 R = H

45 R = Br



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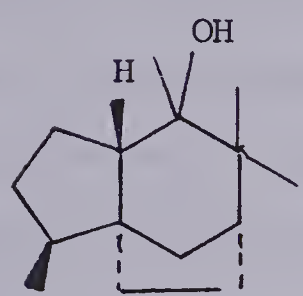

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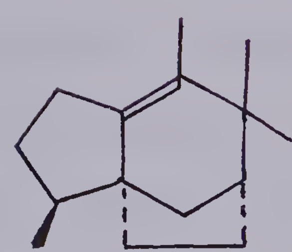

47

44 constituted less than 40% (29). An attempt to invert the stereochemistry of 43 via the corresponding bromide 45 by a kinetically controlled process was completely unsuccessful (29). Secondly, due to the steric congestion at the ketone carbonyl, Wittig reaction could not be effectively employed as a means for the introduction of the required methylene unit; the best yield obtained was less than 10% (26,27). The alternative two-step process, methylation by a Grignard reaction (e.g. 44→46) followed by dehydration, gave, in all cases (22, 26-29), the more stable undesired olefin (e.g. 47) as the predominant product. Although several solutions were provided to this problem (28-31), additional operations were necessary at the expense of overall synthetic efficiency.

We have also been intrigued by the unique structural features of zizaene sesquiterpenes. About two years ago, the synthetic studies presented in part 1 of this thesis were initiated. Khusimone (16) was chosen as the primary target for its considerable industrial importance due to its profound odoriferous properties as well as for its conceivable conversion to other members of the family by subsequent modifications of the ketone carbonyl. With respect to synthetic planning, we envisaged a tricyclic ketone of type 48, accessible, in principle, from the suitably substituted cyclohexenone 49 by an intramolecular photochemical process[3], as an ideal intermediate. Particularly attractive is its potential to overcome the difficulties in stereochemical control encountered by the existing syntheses as described

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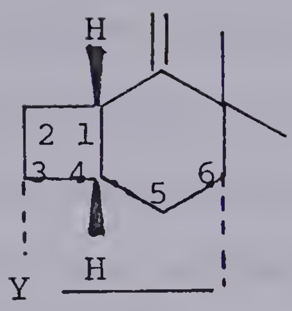
[3]For reviews of photocycloaddition reactions see ref. 33-35.

above. Not only does the stereochemistry at C-1 and C-6 coincide with that of the two crucial centers, C-5 and C-8 respectively, of the natural products by virtue of its mode of formation, but the facile replacement of the ketone carbonyl with a methylene unit (48→50) via the dehydration of alcohol 51 was expected. This mode of dehydration was envisaged since the formation of an endocyclic double bond by the alternative mode of dehydration (51→52) would impose additional angular strain to the already strained cyclobutane ring. It was further anticipated that ring expansion of cyclobutanone 53, derived from olefin 50, to keto ester 54 by the established method (36,37) followed by decarbethoxylation and cyclization would effectively complete the khusimone (16) synthesis. The following sections describe the successful application of such a scheme with necessary modifications leading to the total synthesis of three naturally occurring zizaene sesquiterpenes, (-)-khusimone (16), (-)-epizizanoic acid (14) and (+)-zizanoic acid (9).



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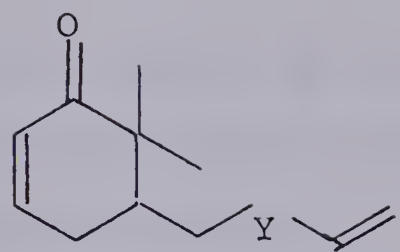

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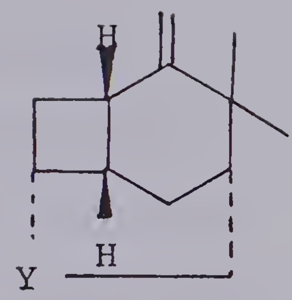

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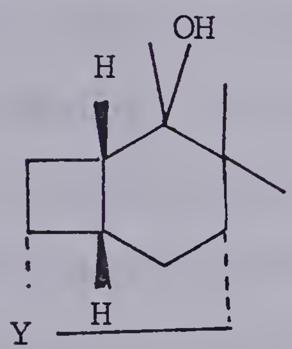

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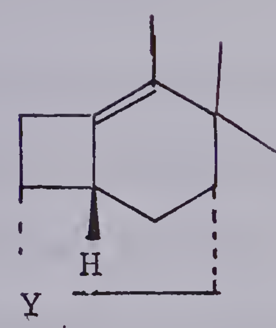

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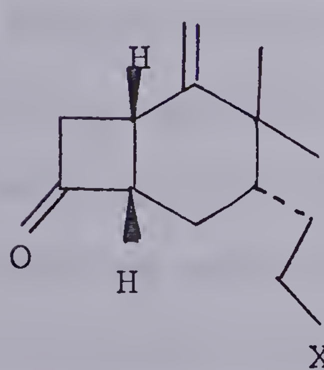

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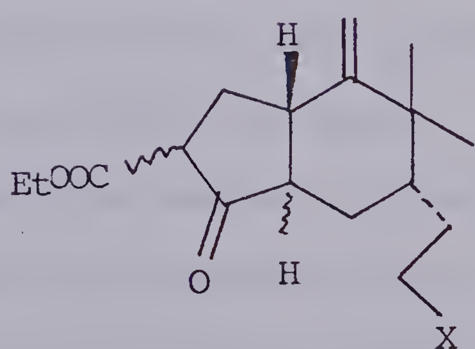

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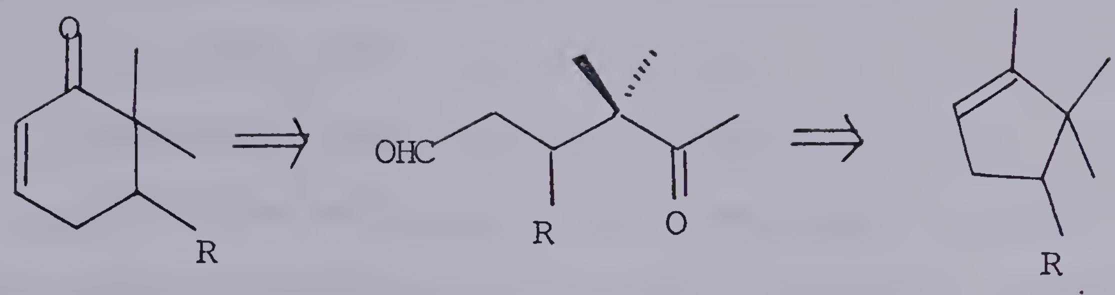
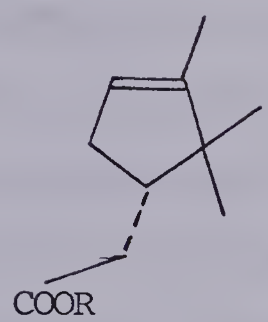
RESULTS AND DISCUSSION

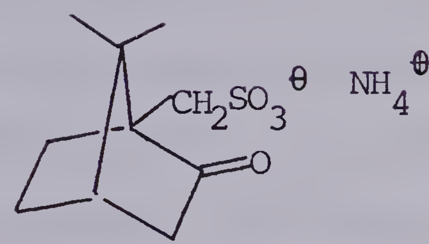
To pursue the synthesis of khusimone (16) according to the described scheme, our immediate task was the preparation of a 6,6-dimethyl-2-cyclohexenone further substituted at C-5 with a functionalized side chain of one- or two- carbon length as represented by formula 55. By the means of retrosynthetic analysis (Scheme 4), the desired cyclohexenone 55 can be obtained by the aldol condensation of keto aldehyde 56 which in turn can be envisaged as the ring cleavage product of a suitably substituted cyclopentene 57. The best known compound possessing the required structural features of 57 is probably α-campholenic acid (58). Its racemate has been previously prepared by Sauers from the sodium salt of 10-camphorsulfonic acid by fusion with solid potassium hydroxide (38). Using the same procedure and the commercially available ℓ-10-camphorsulfonic acid ammonium salt (59) as a starting material, (-)-α-campholenic acid (58) possessing the same chirality as the natural khusimone (16) was obtained in 50% yield. Esterification of acid 58 with potassium carbonate and methyl iodide in refluxing acetone (39) gave a quantitative yield of ester 60 which was subjected to ozonolysis at -78°C in a solution of methylene chloride-methanol (ca. 1:1). Attempted reductive work-up using methyl sulfide as a reducing agent (40) was proven to be ineffective and ozonide 61 was obtained in 42% yield after purification by column chromatography on silica gel eluted with a solution of 20% ether in n-hexane. The structure was apparent from the ir spectrum which



55 56 57

Scheme 4

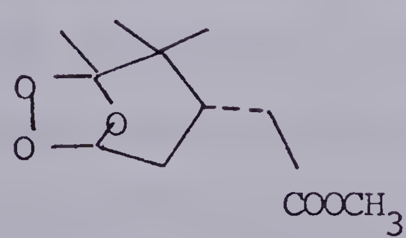




58 R = H

60 R = CH_3

59



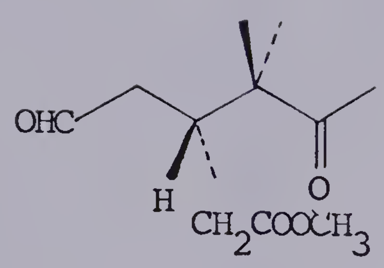
61

showed only the ester carbonyl absorption at 1750 cm^{-1} and the nmr spectrum which displayed in addition to four methyl singlets at δ 0.93, 1.12, 1.36 and 3.58, a narrowly-split (~1 Hz) triplet at δ 5.62 for the methine proton adjacent to the oxygen atoms. On the other hand, when the ozonolysis reaction was worked up after the addition of a more powerful reducing agent, triphenyl phosphine (41), a 75% yield of keto aldehyde (62) was obtained. The ir spectrum showed diagnostic absorption bands at 2840, 2740 (aldehyde), 1735 (ester) and 1705 cm^{-1} (aldehyde and ketone). In the nmr spectrum the two geminal methyl groups coalesced to a six-proton singlet at δ 1.07 whereas the ketone and the ester methyl singlets appeared at δ 2.11 and 3.59 respectively. In addition, the aldehydic proton was observed at δ 9.52 as a triplet with a coupling constant of 1.5 Hz. On treatment with p-toluenesulfonic acid in refluxing benzene, keto aldehyde 62 underwent clean condensation to give enone ester 63 which showed in the ir spectrum a conjugated enone absorption band at 1675 cm^{-1} and that of an ester at 1735 cm^{-1}. In the nmr spectrum, the gem-dimethyl groups appeared at δ 0.94 and 1.11 and the ester methyl at δ 3.61, all as sharp singlets. The β-proton of α,β-unsaturated ketone was displayed as a multiplet centered at δ 6.75 whereas the α-proton appeared at δ 5.86 as a triplet of doublets (J = 10 Hz, J' = 2 Hz). Both mass spectrum, which showed a molecular ion peak at 196.1095, and elemental anlysis were in agreement with the required molecular formula of $C_{11}H_{16}O_3$. Because keto aldehyde 62 was shown to be rather unstable, especially in large scale preparation, it was more practical

to carry out the transformation of 60 to 63 without its purification. The yield of enone ester 63 thus obtained was 70% over three steps.

For the transformation of enone ester 63 to a tricyclic compound of type 48 via an intramolecular photocycloaddition reaction, vinyl ester 64 was an attractive intermediate. Apart from its anticipated ease of preparation from enone ester 63, the cycloaddition of vinyl ester 64 was expected to proceed in a head-to-tail fashion, well precedented by the addition of vinyl acetate to 2-cyclohexenones by an intermolecular photochemical process (33-35), to give product 65 with the desired orientation. The conversion of enone ester 63 into vinyl ester 64 was indeed simple. The latter compound was obtained in 69% yield when the former was trans-esterified with vinyl acetate in the presence of a catalytic amount of mercuric acetate and concentrated sulfuric acid (42). The attempted photocycloaddition of vinyl ester 64 using a variety of conditions was however completely fruitless and resulted in recovery of the starting material. Although the observed unreactivity of vinyl ester 64 remains to be understood, we hoped that the photochemical reaction would take a different course by increasing or reducing its side chain by one atom. Towards this end, allyl ester 66 was synthesized by esterification of the corresponding acid 67 obtained from base hydrolysis of enone ester 63. Disappointingly, allyl ester 66 was found to be equally unreactive. The photochemistry of enone acetate 68, which has a shorter side chain than that of vinyl ester 64, was also examined. This compound was prepared from enone ester 63 in four steps as follows. Enone ester 63 was

was first reduced to diol 69 by lithium aluminium hydride. Oxidation of diol 69 with four equivalents of pyridinium chlorochromate (43) afforded the keto aldehyde 70 which was converted to an epimeric mixture of ketols 71 by treatment with a slight excess of vinyl magnesium bromide at -78 °C. Acetylation of ketol 71 with acetic anhydride in pyridine gave two epimeric keto acetates 68 in a ratio of 1:1 as indicated by the nmr spectrum which showed five methyl singlets at δ 2.00, 1.98 (acetate), 1.11, 1.08 and 0.94 (gem-dimethyl) integrated to a ratio of 1:1:1:1:2. In agreement with the structural assignment, the ir spectrum showed, in addition to an α,β-unsaturated ketone carbonyl absorption band at 1675 cm^{-1}, two ester carbonyl bands at 1738 and 1735 cm^{-1} and the mass spectrum displayed a molecular ion peak at 236.1408. The two epimers were found to be inseparable by column chromatography and since the newly introduced chiral center will be destroyed at a later stage, the epimeric mixture was used for the following photochemical reaction. Irradiation of a methanolic solution of keto acetates 68 for 4 hr caused the complete disappearance of the starting material. The product, obtained in 43% yield, showed in the ir spectrum the appearance of an absorption band at 1700 cm^{-1} and the absence of the 1675 cm^{-1} band previously observed for the conjugated enone system, suggesting that the photocycloaddition had taken place. This was confirmed by the mass spectrum displaying a molecular ion peak at 236.1419 and by the absence of low field signals for olefinic protons in the nmr spectrum. The nmr spectrum showing three sharp methyl singlets at δ 1.00, 1.21 and 1.95 further suggested



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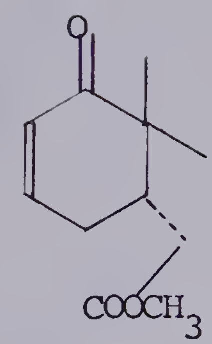

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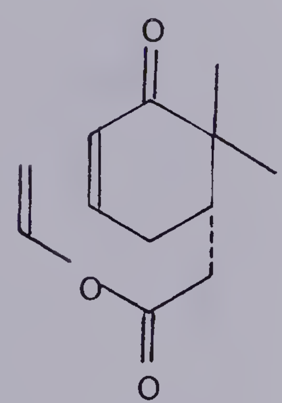

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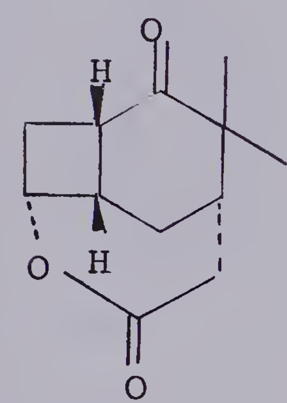

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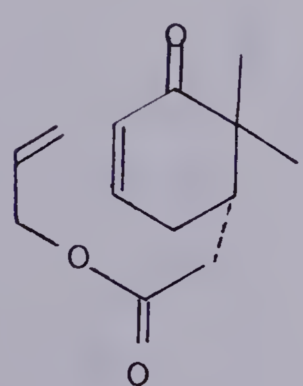

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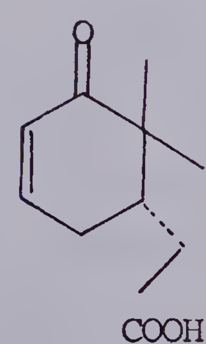

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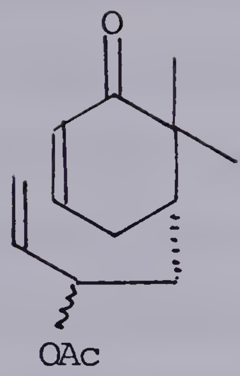

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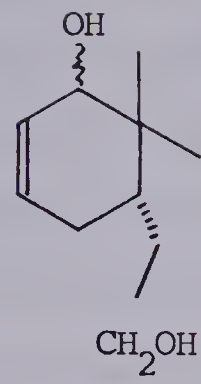

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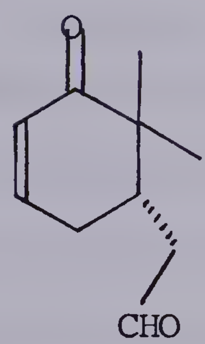

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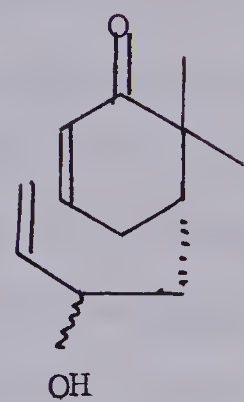

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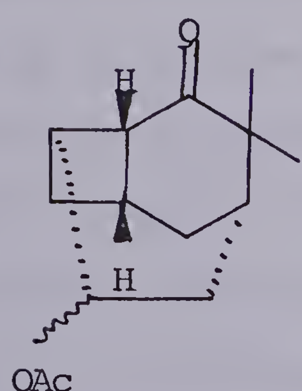
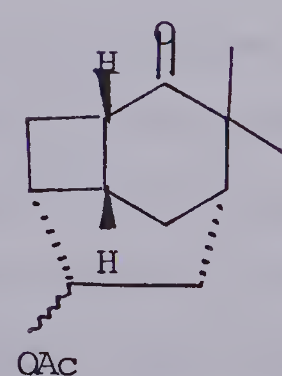
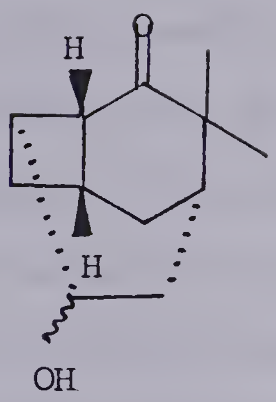


72a



72b

that the product was a single compound which might have resulted from selective isomerization or destruction of one epimer of the starting material during the irradiation. The cycloaddition in principle can proceed in two different ways, head-to-head and head-to-tail, to give adducts 72a and 72b respectively. The available spectral data however did not permit unambiguous definition of the orientation of the isolated product. Nor did the examination of a Dreiding model reveal the preference of one orientation to the other. The conclusive evidence was provided by the following chemical transformations whereby the structure of the product was found to be as depicted in 72a with the undesired orientation. Hydrolysis of the acetate 72a with aqueous sodium hydroxide in refluxing methanol gave the corresponding alcohol 73 which was subsequently oxidized with Jones reagent to the diketone 74. When treated with m-chloroperbenzoic acid in dichloromethane, diketone 74 underwent selective Baeyer-Villiger oxidation to give the lactone 75. Hydrolysis of lactone 75 with aqueous potassium carbonate in refluxing methanol induced concomitant cyclobutane ring cleavage, apparently by a retro-aldol reaction of the intermediate hydroxy ketone 76, giving rise to acid 77. Its structure follows clearly from the spectral analyses. In the ir spectrum, the hydroxy (2500-3200 cm^{-1}), aldehydic C-H stretching (2735 cm^{-1}) and carbonyl (1705 cm^{-1}) absorption bands were observed. The nmr spectrum showed a broad singlet at δ 9.76 diagnostic for the aldehydic proton whereas a molecular ion peak was displayed at 226.1207 in the mass spectrum consistent with the required formula of $C_{11}H_{18}O_4$. The assignment



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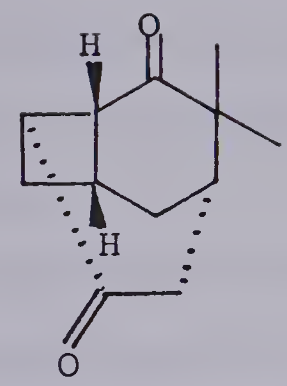

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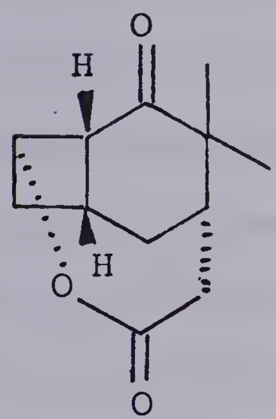

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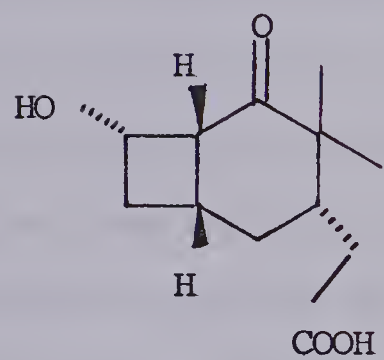

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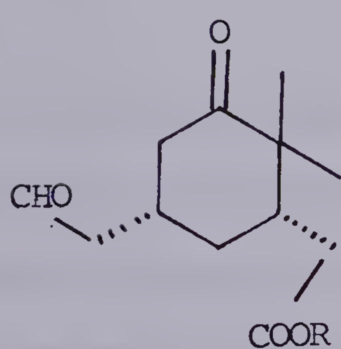
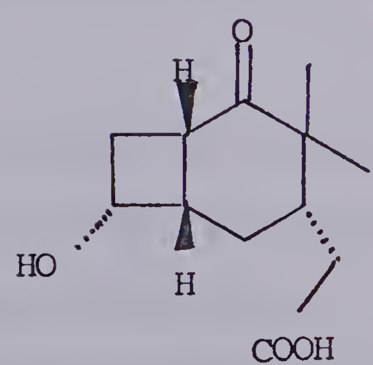


77 R = H

78 R = CH_3



79

was further confirmed by the conversion of acid 77 to its methyl ester 78 using diazomethane. It is noted that by the above reaction sequence, the alternative photochemical product 72b should result in the formation of stable hydroxy acid 79 and the isolation of acid 77 clearly defines the structures of its precursors as depicted.

Although it would be of general interest to investigate the photochemistry of other suitable derivatives of keto ester 63 such as 80 and 81 in particular, the large number of steps required for their synthesis as well as for the later modification preclude their efficient application of khusimone (16) synthesis. The subsequent studies were focussed on the addition, in a head-to-tail manner, of a latent ketene unit to the double bond of keto ester 63 by an intermolecular photochemical process. We realized at the outset that such an approach would not allow profound stereochemical control as the addition could take place from both the α and the β face of the molecule and hence adjustment of stereochemistry at a suitable stage would be necessary. This drawback could however be compensated to a certain extent as enone 63 could be used directly without modifying its ester side chain.

Due to its availability, vinyl acetate was initially used as a ketene equivalent. Irradiation of enone 63 with twenty-fold excess of vinyl acetate in benzene for 3 hr at room temperature afforded a mixture of inseparable photoadducts. The ir spectrum of the mixture exhibited absorption bands at 1698 and 1735 cm^{-1} clearly indicating the presence of ester and saturated ketone groups. The formation of

1:1 adduct was substantiated by the mass spectrum which showed a molecular ion peak at 282.1462. The nmr spectrum was complex and displayed two singlets for the acetoxy group suggesting the presence of at least two isomers. In fact, as shown by the subsequent transformation both regioisomers 82 and 83 were formed in a ratio of approximately 4:1 with the desired isomer 82 predominanting. On treatment with sodium methoxide in methanol at room temperature for 30 min, the mixture of photoadducts gave two products readily separable by column chromatography on silica gel. The minor component isolated in 16% yield was readily deduced to be a mixture of aldehyde 78 and its C-5 epimer 84 resulting, apparently, from the undesired photoadduct 83. The major component which was obtained in 65% yield was shown to be a mixture of diastereomeric alcohols 85[4] derived from the desired head-to-tail adducts 82 as follows. In addition to an alcohol absorption at 3450 cm^{-1}, the ir spectrum showed saturated ketone and ester carbonyl absorption bands at 1702 and 1738 cm^{-1} respectively. In the nmr spectrum, the appearance of six singlets in the region of δ 0.90-1.21 for a total of six protons was indicative of the presence of at least three stereoisomers. Furthermore, Jones oxidation of this mixture gave two separable ketones 86 and 87 in a ratio of 5:6 and in a total yield of 69%. The major product was crystallized as solid (m.p. 127-128 °C) from ether whereas the minor isomer was isolated as a thick colorless oil. The ir and mass spectra of these ketones were very

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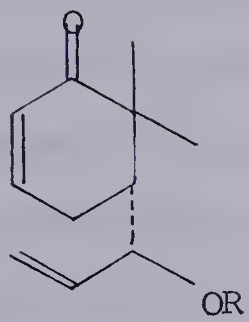
[4]Based on previous observations (44), a cis ring junction could be readily assigned to each diastereomer.



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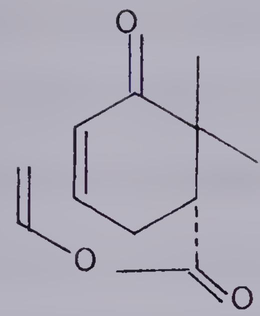

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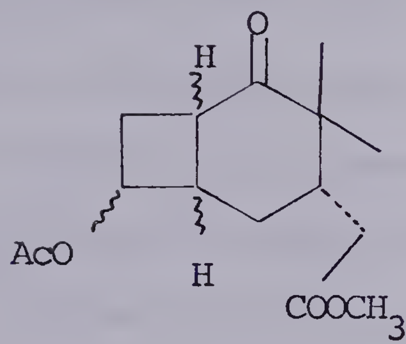

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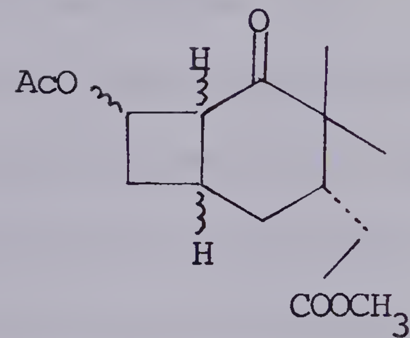

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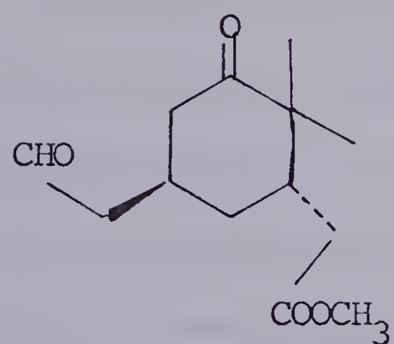

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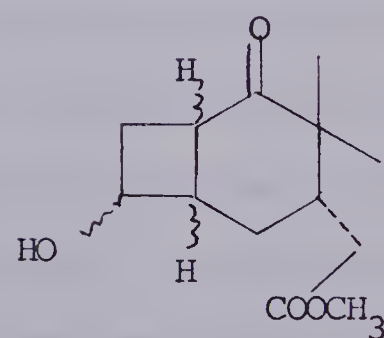
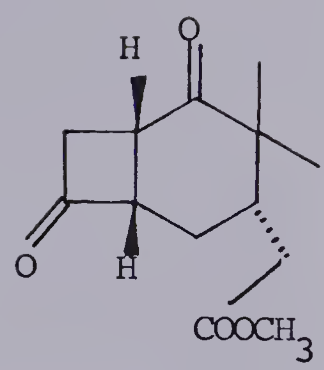


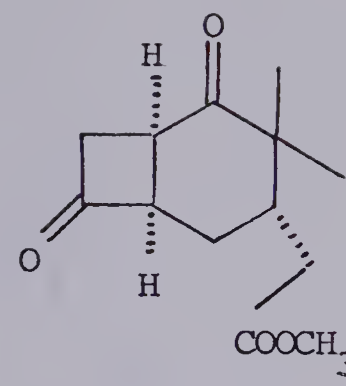
85

similar. In each of the ir spectra, carbonyl absorption bands were observed at 1785 (four-membered ketone), 1738 (ester) and 1710 cm^{-1} (six-membered ketone) and the mass spectrum of each isomer exhibited a molecular ion peak at 238.1204 consistent with the formula of $C_{13}H_{18}O_4$. However, distinct differences were observed in their nmr spectra. The geminal methyl groups of the major product appeared as a pair of singlets at δ 1.06 and 1.12. Whereas the minor product showed two singlets at δ 0.97 and 1.21 for the corresponding methyls. The difference in $\Delta\delta$ (0.24 for the minor vs 0.06 for the major) observed for the gem-dimethyl groups of these two compounds allowed us to tentatively assign their stereochemistry as follows. An examination of Dreiding model reveals that in the most stable contributive conformation of compound 86, which could be represented by 86a, one methyl group lies within the deshielding zone of cyclohexanone carbonyl and the other within the shielding zone of cyclobutanone. On the other hand, in the case of compound 87, whose stable conformation is depicted in formula 87a, both methyls are distant from the cyclobutanone ring and thus devoid of any serious influence from its carbonyl. A larger $\Delta\delta$ for 86 and a smaller one for 87 are therefore expected and it follows that the minor isomer possesses structure 86 and the major structure 87. These structural assignments were further supported by the optical rotatory dispersion (O.R.D.) analysis (45, 46). The minor isomer displayed a positive anomalous single Cotton effect curve (Fig. 1) and the major showed a negative one (Fig. 2). With the aid of models, the octant diagrams corresponding to the most



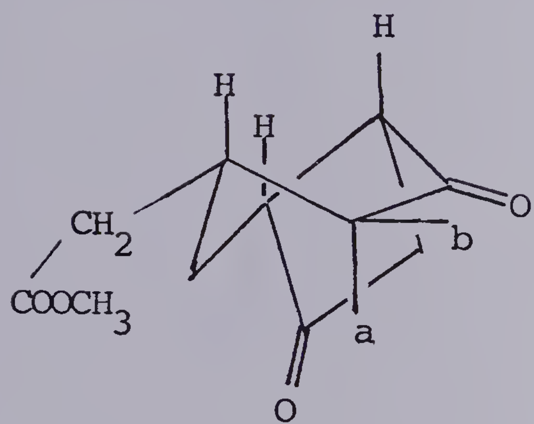
H
O
O
H
COOCH3

86



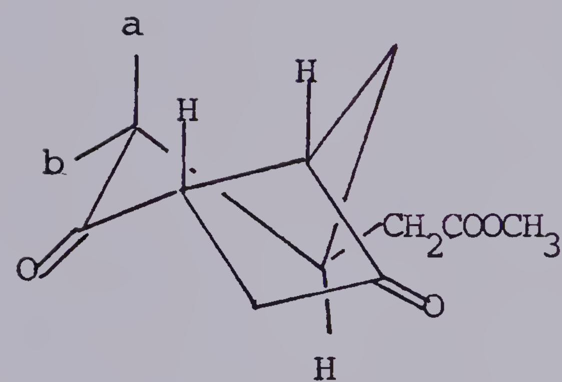
H
O
O
H
COOCH3

87



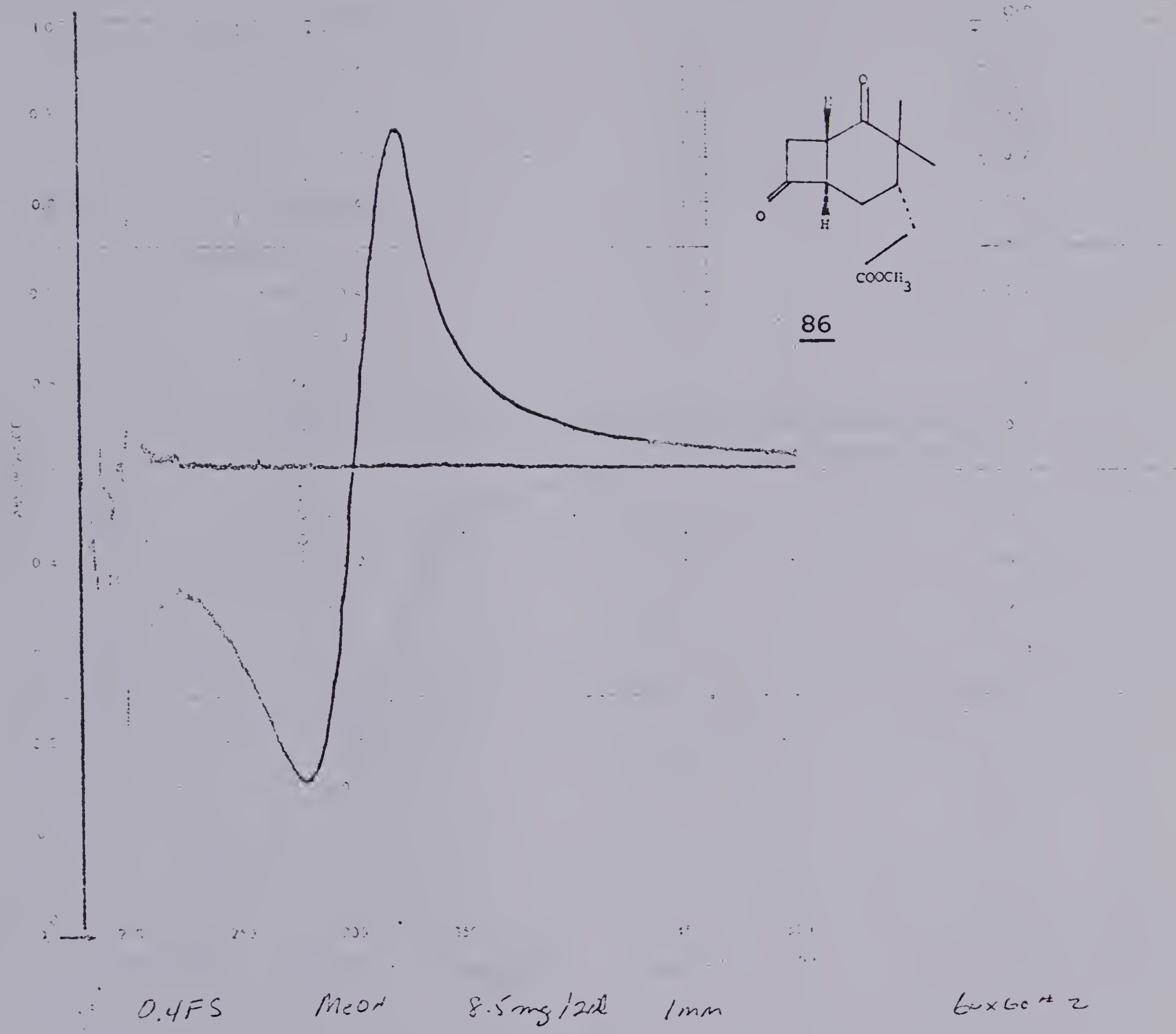
H
H
H
CH2
COOCH3
O
b
a
O

86a



a
H
H
b
O
CH2COOCH3
O
H

87a



86

Fig. 1. Optical rotatory dispersion curve of diketone 86

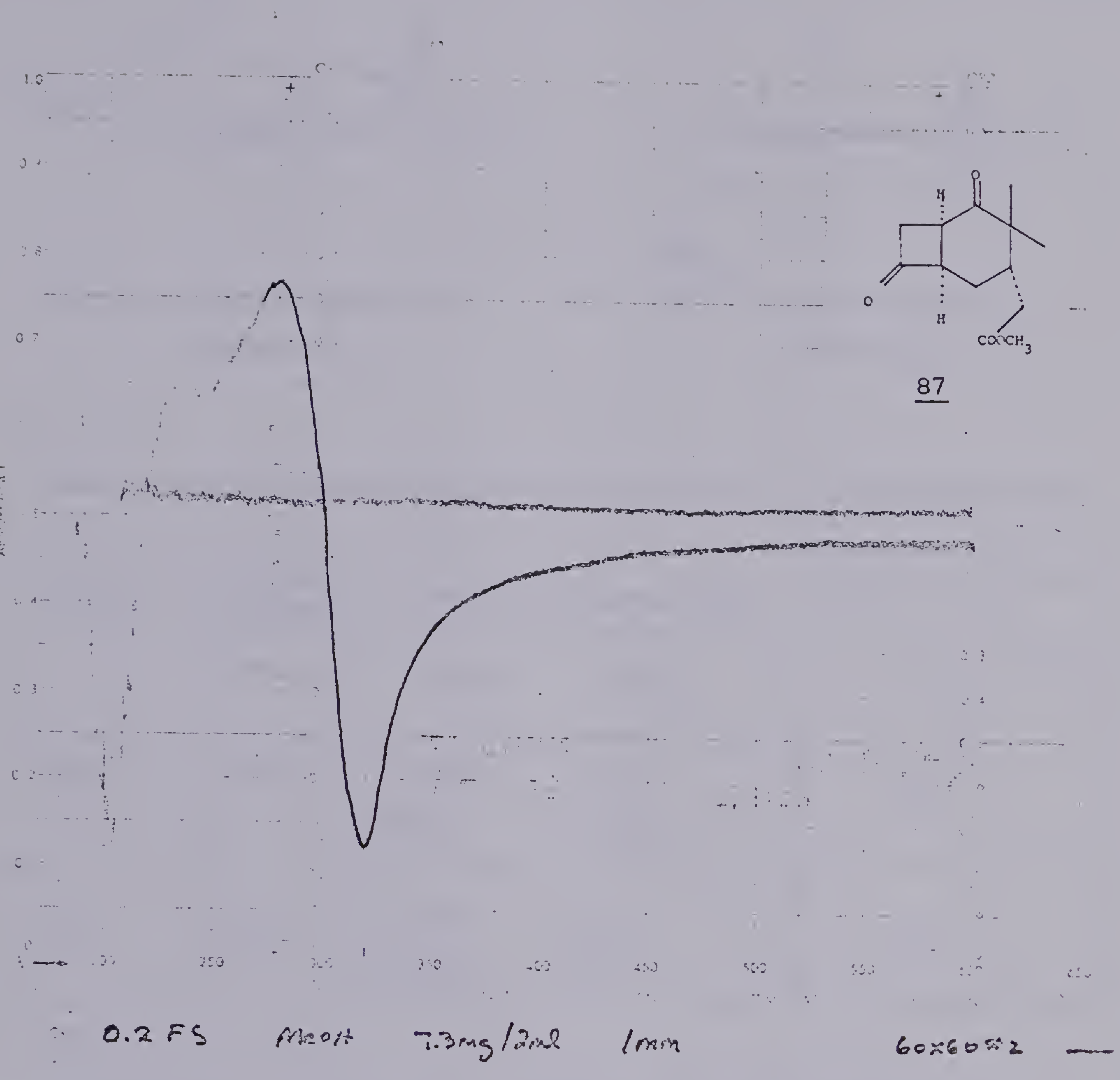


Fig. 2. Optical rotatory dispersion curve of diketone 87

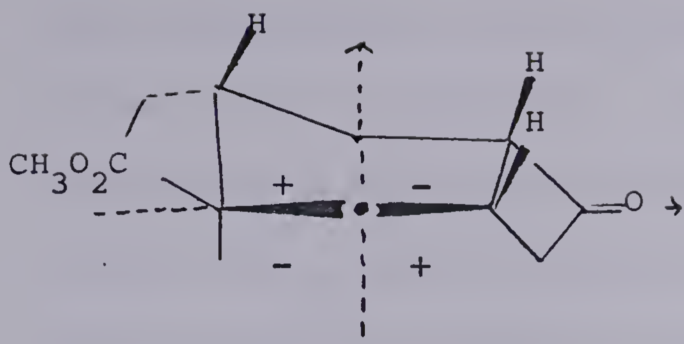


Fig. 3. Octant diagram of diketone 86

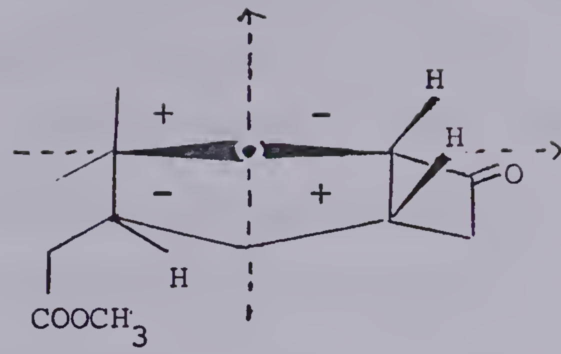


Fig. 4. Octant diagram of diketone 87

Table 1. Optical rotation dispersion properties of compounds 86 and 87

compound	specific rotation $[\alpha]_D$	molecular rotation (deg.) $[\Phi]_{320}$	$[\Phi]_{278}$	molecular amplitude* $a = \frac{[\Phi]_1 - [\Phi]_2}{100}$
86	+119.5	+17024 peak	-15679 trough	327
87	-126.4	-4164 trough	+2959 peak	-169

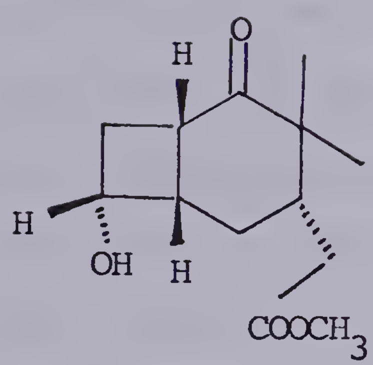
*The molecular amplitude, a, is defined as the difference between the molecular rotation at the extremum (peak or trough) of longer wavelength $[\Phi]_1$ and the molecular rotation at the extremum of shorter wavelength $[\Phi]_2$, divided by 100.

stable conformations of the two diastereomers 86 and 87 are represented by Fig. 3 and 4 respectively. In the case of 86 (Fig. 3), since the large ester side chain occupies the positive octant at upper left position while the four-membered ring and the two methyl groups are more less equally distributed among the positive and the negative octants, the octant rule predicts unambiguously a positive Cotton effect and indeed this was observed. In contrast, the Cotton effect of isomer 87 (Fig. 4) is less predictable as the cyclobutanone ring and the ester chain are expected to exert opposing effects while two methyl substituents occupy two adjacent octants. It was especially gratifying to find that the major isomer showed a negative Cotton effect, eliminating its alternative structure of 86 (and thus confirming its structural assignment of 87). The optical rotation dispersion properties of these two diastereomers are compiled in Table 1 which also summarizes the molecular amplitude of each compound. The observation that compound 86 showed a molecular amplitude far greater than that of its isomer 87 was in full support of the above analysis of substitution effect.

An attempt was also made to resolve the stereochemical enigma by chemical methods. The general strategy was to selectively reduce the cyclobutanone carbonyl of 86 to an α hydroxy group followed by the formation of a lactone ring to confirm the *cis*-relationship of the ester group and the cyclobutane ring. Selective reduction of diketone 86 was carried out at 0°C in tetrahydrofuran using one equivalent of lithium tri-tert-butoxyaluminium hydride. The keto alcohol 88 thus

obtained showed in the ir spectrum, a hydroxyl absorption band at 3450 cm^{-1} superseding the four-membered ketone carbonyl absorption (1785 cm^{-1}) of the starting material. Its nmr spectrum displayed three sharp methyl singlets at δ 3.68, 1.11 and 1.07 indicating a single epimer most likely formed by the addition of the bulky reducing agent from the sterically less hindered β face of the starting material. Attempted lactonization of alcohol 88 was however unsuccessful. When basic condition (sodium hydride in 1,2-dimethoxyethane) were used, alcohol 88 was recovered intact even after prolonged treatment (24 hr) at elevated temperature. On the other hand, when it was treated with p-toluenesulfonic acid in refluxing benzene, a complex mixture was formed. Its nmr spectrum showed signals at δ 5.20 suggesting the presence of olefinic product possibly compound 89 but the absence of signal in the δ 4-5 region anticipated for the methine proton adjacent to the lactone oxygen atom of the desired product 90. To ascertain that the negative results were not due to the incorrect structural assignments, diketone 87 was also reduced with lithium tri-tert-butoxy-aluminium hydride and the product 91 was subjected to lactonization. As expected, under various conditions the lactone ring was not formed. Although the attempted chemical proof was non-constructive, the structural assignments of diketones 86 and 87 based on the physical methods were sufficiently convincing. The correctness of these assignments was confirmed by the subsequent transformations.

To facilitate further discussion, the above results are summarized below. Photocycloaddition of enone 63, prepared from 10-ℓ-camphor-



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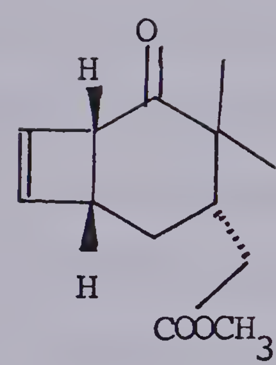

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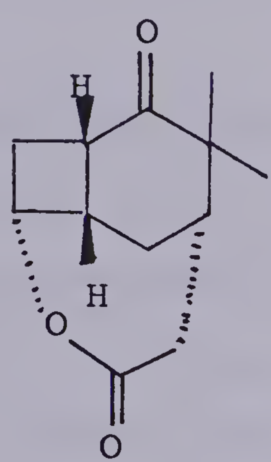

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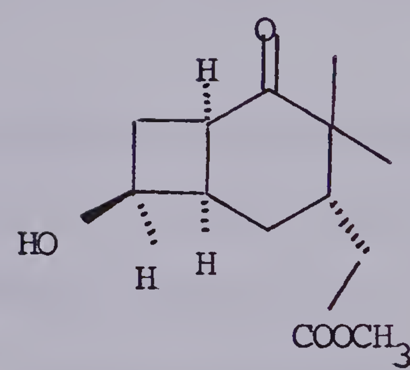

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sulfonic acid ammonium salt (59) in four steps and in 35% yield, to vinyl acetate followed by base hydrolysis of the adducts gave diastereomeric alcohols 85. Oxidation of this mixture with Jones reagent resulted in the formation of diketones 86 and 87 in a ratio of 5:6 and in a total yield of 45% from enone 63.

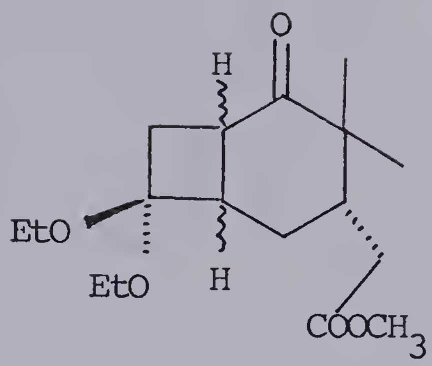
The transformation of enone 63 into diketones 86 and 87 was improved considerably when 1,1-diethoxyethane (47) was later used as a ketene equivalent. Its photocycloaddition to enone 63 in benzene proceeded in a completely regioselective manner to give an inseparable mixture of at least two diastereomers (four sets of partially superimposed $-OCH_2-$ quartets at δ 3.39 region in the nmr spectrum) of the desired adduct 92 in near-quantitative yield. This mixture when treated with diluted hydrochloric acid in acetone gave, as the only products, diketones 86 and 87 in the ratio of 5:8 and in a total yield of 80%.

Of the two diketones 86 and 87, only the former is synthetically useful. To enhance the efficiency of synthesis, it is highly desirable to invert the stereochemistry of both ring junction carbons of the latter compound. In principle, this could be directly accomplished by a process of double epimerization since each of the chiral centers in question is α to a ketone carbonyl. In practice, it was found not to be the case, under a variety of reaction conditions the starting material was recovered intact. The inertness of the compound was, however, not totally surprising and could be readily attributed to its inability to undergo first-stage epimerization at either center to

give the corresponding trans-fused compound which is expected to be thermodynamically far less stable (44). An alternative approach which is conceivable for the conversion of diketone 87 to its diastereomer 86 involves a two-step sequence - dehydrogenation and hydrogenation. This was successfully applied. Although initial attempts to oxidize diketone 87 with standard oxidizing agents such as dichlorodicyanoquinone and selenium dioxide were fruitless, its treatment with two equivalents of pyridinium bromide perbromide in acetic acid induced consecutive bromination and dehydrobromination to give an inseparable mixture of enediones 93 and 94. The ratio of these two compounds was estimated to be 4:1, with the former predominanting, on the basis of the nmr spectrum which displayed two pairs of methyl singlets, one pair at δ 1.28 and 1.08 and the other at δ 1.22 and 1.08, integrated to a ratio 1:4 as well as a broad singlet (1/6 of major methyl signals) at δ 5.44 for the vinylic proton of isomer 93. The mass spectrum exhibited a molecular ion at 236.1048 in agreement with the structural assignments. Interestingly, in the ir spectrum, while the cyclohexanone absorption band of the starting material at 1710 cm^{-1} shifted as expected to 1695 cm^{-1} due to conjugation, the four-membered ketone carbonyl absorption remained virtually unchanged at 1785 cm^{-1}. Reduction of the mixture of enediones 93 and 94 by treatment with zinc dust in acetic acid occurred smoothly at room temperature and afforded a 3:2 ratio of diketones 86 and 87 in 65% yield. The latter compound, in principle, could be recycled. In practice, by the photochemical process immediately above involving a single isomerization operation,

the desired diketone 86 was obtained in 45% yield from enone 63.

Prior to the conversion of six-membered ketone carbonyl of diketone 86 to a methylene unit required for the synthetic target, its cyclobutanone was protected. While standard ketalization condition, i.e. ethylene glycol and p-toluenesulfonic acid in refluxing benzene, showed little selectivity and gave rise to diketal 95 as the major product, transketalization of diketone 86 with 2-ethyl-2-methyl-1,3-dioxalane in refluxing benzene in the presence of a catalytic amount p-toluenesulfonic acid (48) resulted in the formation of the desired ketal 96 in 85% yield. Initial attempts to replace its ketone carbonyl with a methylene group directly by Wittig reaction proved to be fruitless due to steric hinderance. As a result, a two-step sequence via Grignard reaction and dehydration was sought. Towards this end, ketal ester 96 was hydrolyzed with aqueous sodium hydroxide. The acid 97 thus obtained was treated with five equivalents of methyl magnesium bromide at room temperature and the resulting mixture was subjected to treatment with diazomethane in ether prior to purification. Apart from a 40% yield of the desired ester 98, diol 99 amounting to a 25% yield was also isolated. The formation of this by-product was readily attributable to the concomitant reaction of the carboxyl group with the excess of the Grignard reagent over the relatively long period of reaction time which was required for the completion of the reaction due to the low reactivity of the ketone carbonyl. This difficulty was completely eliminated when acid 97 was first converted to the corresponding sodium salt with one equivalent of sodium hydride prior to the addition of methyl magnesium bromide. By a similar reaction sequence



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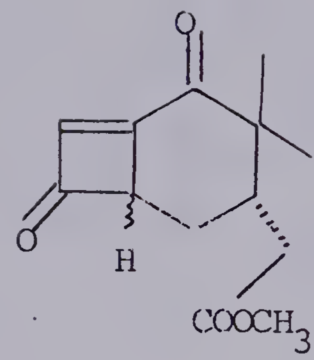

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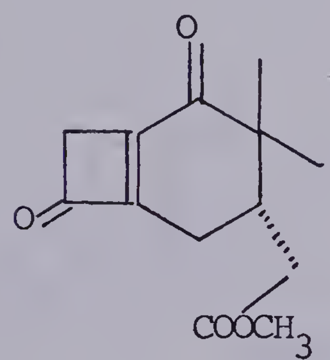

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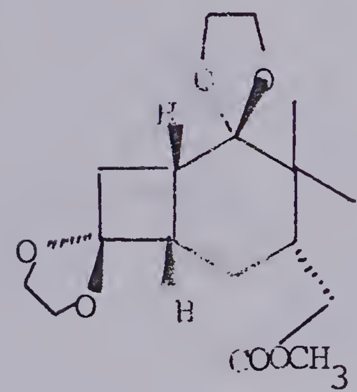

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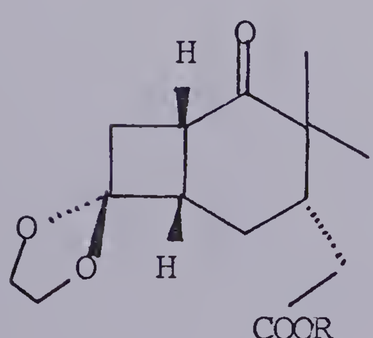

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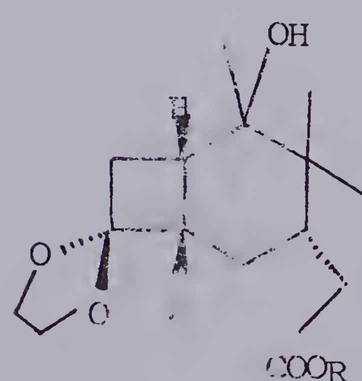
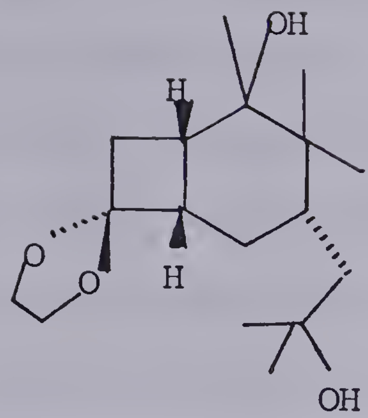
97 R = H



98 R = CH_3

104 R = H



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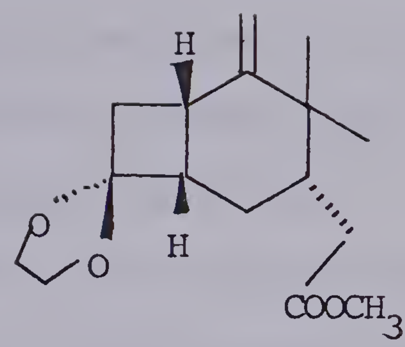

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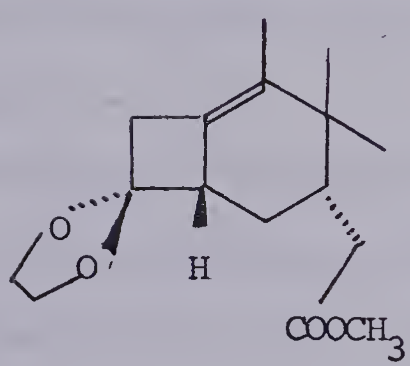

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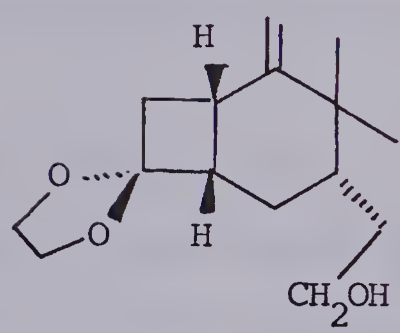

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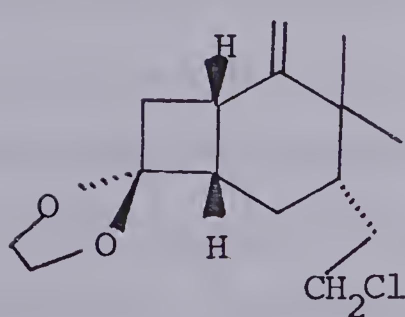

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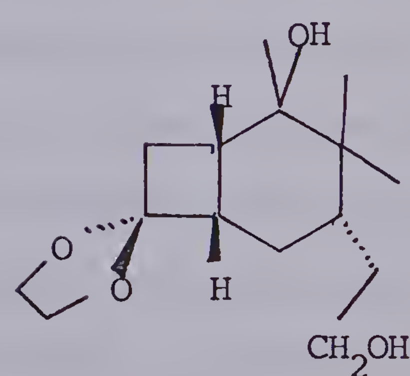

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as before, the desired ester 98 was isolated in 64% yield along with a 19% recovery of the starting material without the formation of diol 99 in any detectable quantity. The ester 98 when subjected to treatment with thionyl chloride and pyridine in benzene underwent clean dehydration giving an 89% yield of olefin 100, which showed two singlets at δ 4.78 and 4.96 in the nmr spectrum and absorption bands at 3100, 1630 and 890 cm^{-1} in the ir spectrum in full agreement with the presence of an exocyclic double bond. The reaction was found to be completely regioselective; no detectable amount of olefin 101 was formed via the alternative mode of dehydration. The exclusive formation of one olefin was in accord with the expectation discussed previously.

Olefin 100 was subsequently reduced with lithium aluminium hydride in tetrahydrofuran at room temperature to give alcohol 102 in near-quantitative yield. Treatment of this alcohol with phosphorus oxychloride in pyridine gave rise to a 75% yield of the corresponding chloride 103 which showed, in the ir spectrum, olefinic absorption at 1630 cm^{-1}. In the nmr spectrum, the olefinic protons appeared as two singlets at δ 4.75 and 4.92 and the methylene group bearing the chlorine atom resonated at δ 3.50 as a multiplet. The structure was confirmed by the mass spectrum displaying two molecular ion peaks at 270.1380 (Cl^{35}) and 272.1362 (Cl^{37}) with a relative intensity of ca. 3:1 respectively. Chloride 103 could be conceivably prepared by reduction of the hydroxy acid 104, derived from the keto acid 97, followed by treatment of the resulting diol 105 with a suitable reagent

which would effect the dehydration of its tertiary alcohol and the replacement of its primary hydroxyl group with a chlorine atom. In this way the synthesis could be shorten by two steps. To test its feasibility, the mixture obtained from the Grignard reaction of the sodium salt of acid 97 was reduced with lithium aluminium hydride. The direct conversion of diol 105 to chloride 103 was attempted under various conditions using phosphorus oxychloride or thionyl chloride as reagents. In all cases, a complex mixture was obtained and the best yield of the desired compound amounted to ca. 10%.

Having incorporated the required methylene group and a proper side chain for the formation of ring C of the target molecule, khusimone (16), our immediate concern was the expansion of the cyclobutane ring of chloride 103 to the required five-membered one. Treatment of chloride 103 with aqueous hydrochloric acid in acetone resulted in the hydrolysis of its ketal blocking group to give, quantitatively, ketone 106. This ketone was subjected to one-carbon ring expansion with ethyl diazoacetate and boron trifluoride etherate in ether (36). The reaction was found to be complete after 1 hr at 0°C and 4 hr at room temperature and two products were obtained in a ratio of 2:1 and a total yield 86%. Assignment of structure 107 to the major product and 108 to the minor was made as follows. The isomeric nature of these two compounds as well as their gross structure (without specifying the location of the ketone and the ester group) were clearly indicated by the ir spectra which showed, in each case, absorption bands at 1760 and 1735 cm^{-1} characteristic of cyclopentanone and ester functionalities

respectively and by mass spectra in which each displayed molecular ion peaks at 312.1490 and 314.1445 consistent with the required formula of $C_{17}H_{25}O_3Cl$. In the nmr spectra, the vinylic protons of the major isomer resonated at δ 4.90 as a broad singlet and those of the minor product appeared as two singlets at δ 4.72 and 4.98, clearly indicating that the exocyclic double bond in each case was intact during the transformations. The regiochemistry of these two compounds was tentatively assigned based on previous observations in this laboratory (36,37) that the boron trifluoride catalyzed homologation of cycloalkanone with ethyl diazoacetate proceeded, without a single exception, in a regioselective manner with the preferential migration of the less substituted α-carbon atom. These assignments were substantiated by the following transformation of the major isomer to (−)-khusimone (16).

The conversion of keto ester 107 to (−)-khusimone (16) requires two chemical processes: decarbethoxylation and cyclization. These were effected by a single operation and a 61% yield of (−)-khusimone (16) was obtained after keto ester 107 was treated with aqueous sodium hydroxide in refluxing methanol for 40 min[5,6]. The totally synthetic

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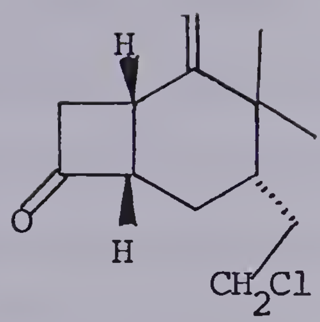
[5]It was necessary to bring the solution into reflux rapidly using a pre-heated oil bath. Otherwise a substantial amount of keto ether was formed.

[6]Under the same conditions, the minor ring expansion product gave rise to a complex mixture in which (−)-khusimone was found to be absent. These results were in agreement with its structural assignment.



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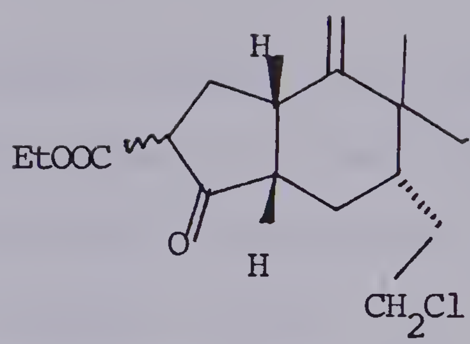

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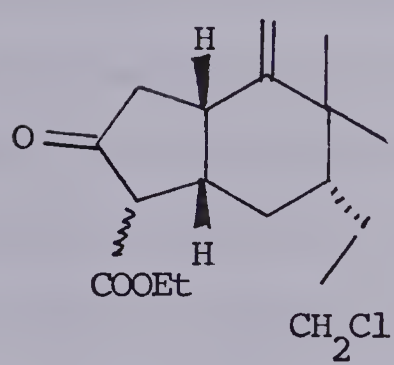

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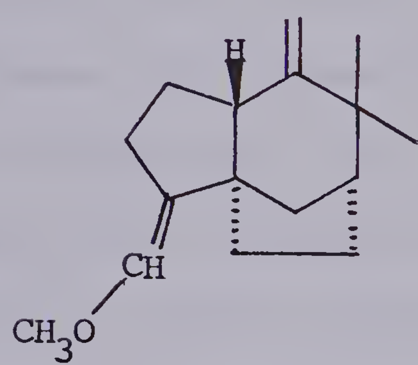

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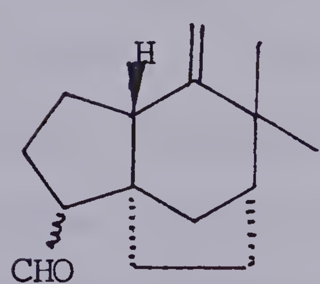

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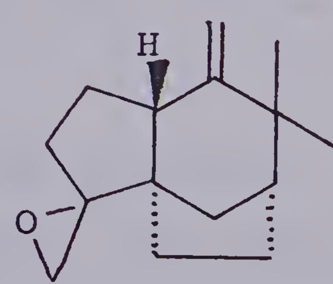


111

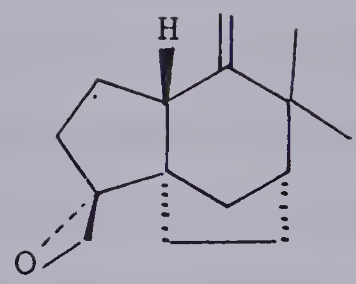
material was shown to be identical with the natural product in all respects including ir, nmr and mass spectra, thin-layer chromatographic behavior, m.p. and specific rotation.

Following the completion of (-)-khusimone synthesis, our efforts were directed towards its extension to the synthesis of other zizaene sesquiterpenes possessing the normal fifteen-carbon skeleton with (+)-zizanoic acid (9)and its (-)-epimer 14 as specific targets. The transformation of (-)-khusimone to the two compounds requires the replacement of its ketone carbonyl with a carboxyl group preferably in a completely stereoselective manner. An obvious approach to introduce the required functionalized one-carbon unit is by a Wittig reaction using methoxymethyl triphenylphosphorane ylide followed by hydrolysis of the resulting enol ether 109 to aldehyde 110. The latter reaction however often requires strongly acidic conditions which may also effect the isomerization of the unstable exocyclic double bond into the ring. Alternatively, the aldehyde of type 110 could also be prepared by Lewis acid catalyzed isomerization of epoxide 111 (49) which in turn could be directly derived from the corresponding ketone by addition of a suitable sulfur ylide (50). The latter route was successfully explored as follows.

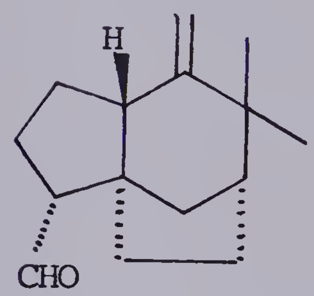
The synthetic (-)-khusimone, when treated with an excess of dimethyl sulfonium methylide (50) in tetrahydrofuran, gave a 51% yield of a single epoxide 112 which showed in the nmr spectrum two doublets centered at δ 2.67 and 2.53 readily attributable to the methylene protons of the epoxy ring and the absence of carbonyl absorption in

the ir spectrum. In agreement with required formula of $C_{15}H_{22}O$, a molecular ion peak at 218.1674 was displayed in the mass spectrum. Since the addition of the ylide should occur preferentially from the sterically less hindered β face of the molecule, its stereochemistry was assigned accordingly. The desired rearragement of epoxide 112 was effected by brief treatment (1 hr) with boron trifluoride etherate in ether at 0°C. The aldehyde 113 thus obtained, in quantitative yield, showed in the ir spectrum the characteristic aldehyde absorption bands at 2710 and 1720 cm^{-1}. The nmr spectrum displayed a doublet at δ 9.73 for the aldehydic proton and two singlets at δ 4.80 and 4.60 indicating that the exocyclic double bond was unaffected. The assignment of an α configuration to the aldehyde group was precedented by ample examples (51) which showed that the rearrangement of epoxide proceeded with inversion of stereochemistry. Jones oxidation of the aldehyde 113 afforded a 77% yield of (-)-epizizanoic acid (14) whose ir and nmr were found to identical with those of the natural product.

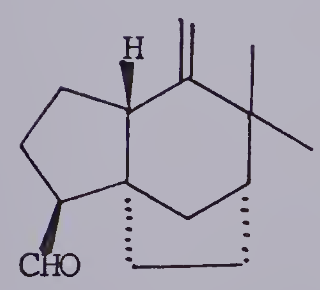
Aldehyde 113 underwent epimerization on treatment with dilute sodium hydroxide in methanol and an equilibrium mixture consisting of five parts of α-epimer 113 and seven parts of β-epimer 114 was established after 9 hr at room temperature. These two epimeric aldehydes were separable by column chromatography. The newly formed aldehyde 114 was oxidized to (+)-zizanoic acid (9) in 90% yield when treated with Jones reagent. The equivalence of the synthetic and the naturally occurring material was established by comparison



112



113



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of their ir and nmr spectra.

In conclusion, three sesquiterpenes of the zizaene family, khusimone (16), epizizanoic acid (14) and zizanoic acid (9) have been synthesized in optically active form from the ammonium salt of (-)-ℓ-10-camphorsulfonic acid (59) in sixteen, nineteen and twenty steps respectively. Since zizaene (8) and khusimol (13) have previously been prepared from zizanoic acid (9) (6), the described approach also represents a formal total synthesis of these two sesquiterpenes.

EXPERIMENT

General

Melting points were determined on Kofler hot stage apparatus and are uncorrected. Optical rotations were measured by Perkin-Elmer 141 polarimeter. Infrared (ir) spectra were obtained by using Perkin-Elmer model 457, 337 spectrophotometer and Nicolet 7199 Fourier transform spectrophotometer. Unless otherwise stated, ir samples were run as thin films. Nmr spectra were recorded on Varian A-60, HR-100 and 90 MHz Perkin-Elmer 32 spectrometers. Unless otherwise stated, carbon tetrachloride was used as solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra were recorded on AEI MS-50 mass spectrometer. Elemental analyses were performed by the microanalytical laboratory of this department. Jasco ORD/UV-5-SS-20-2 was used to measure optical rotary dispersion.

Materials

Acetone was treated with potassium permanganate, dried over anhydrous potassium carbonate and distilled. Dichloromethane used for reactions was distilled from phosphorus pentoxide. Methanol was dried over magnesium turnings at elevated temperature for 2 hr and distilled. Ether, tetrahydrofuran, 1,2-dimethoxyethane and benzene were freshly distilled from lithium aluminium hydride. Ozone was generated with a Welsbach ozonator. Ammonium salt of (-)-ℓ-10-camphorsulfonic acid was obtained from Aldrich Chemical Company.

Silica gel, 0.15-0.33 mm granulation, was used as adsorbent for column chromatography. Thin-layer chromatography (tlc) was carried out using Merck Kieselgel G (type 60).

(-)-α-campholenic acid (<u>58</u>)

To the fused potassium hydroxide (120 g, 2.14 mol) in a porcelain casserole, was added slowly with stirring the ammonium salt of (-)-α-10-camphorsulfonic acid (100 g, 0.40 mol). After the completion of the addition (<u>ca.</u> 25 min), the molten mass was heated for an additional period of 15 min. Upon cooling, the mass was dissolved with water (800 ml). After extraction with ether (200 ml) and dichloromethane (400 ml), the aqueous solution was acidified with ice-cold dilute hydrochloric acid and extracted with ether (300 ml) and dichloromethane (2 x 300 ml). The organic solution was dried ($MgSO_4$) and filtered. After most of the solvent was removed under the reduced pressure, the viscous residue was distilled to give pure acid <u>58</u> (35.4 g, 52% yield) : b.p. 97°C/0.65 torr; $[\alpha]_D^{25} = -9.0°$ (c = 1.1, $CHCl_3$); ir 3200-2500 and 1708 cm^{-1} (acid); nmr δ 11.48 (br. s, 1H, -COOH), 5.20 (br. s, 1H, -HC=), 1.60 (br. s, 3H, $\underline{CH_3}$-CH=), 0.98 (s, 3H, $-CH_3$) and 0.79 (s, 3H, $-CH_3$); mass spectrum M^+ 168.1142 (Calcd. for $C_{10}H_{16}O_2$: 168.1150).

Methyl α-campholenate (<u>60</u>)

A mixture of α-campholenic acid (<u>58</u>) (2.02 g, 12 mmol) and potassium carbonate (4.14 g, 30 mmol) in acetone (20 ml) was stirred

at room temperature for 2 hr. Methyl iodide (37 ml, 60 mmol) was introduced by syringe and the reaction mixture was refluxed overnight. After most of the solvent was evaporated under the reduced pressure, water was added and the organic product extracted by dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness. Bulb-to-bulb distillation (100° /2 torr) of the residue gave the methyl ester 60 (2.17 g, 100% yield) : ir 1745 cm^{-1} (ester); nmr δ 5.20 (br. s, 1H, -CH=), 1.58 (br. s, 3H, CH_3C=), 0.98 (s, 3H, $-CH_3$) and 0.75 (s, 3H, $-CH_3$); mass spectrum M^+ 182.1308 (Calcd. for $C_{11}H_{18}O_2$: 182.1306).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.46; H, 10.12.

5-Carbomethoxymethyl-6,6-dimethyl-2-cyclohexenone (63)

At -78°C, ozone (condition: E = 80 V, air inlet = 8 psi, ozone outlet = 0.06 psi) was allowed to pass through a solution of the ester 60 (23.58 g, 0.13 mmol) in dichloromethane (65 ml) and methanol (60 ml) until a light blue color retained. The mixture was warmed up gradually to about -25°C under a nitrogen atmosphere and triphenylphosphine (34 g, 0.13 mol) was added. After removal of the solvent, the crude keto aldehyde [ir 2840, 2740 (aldehyde), 1735 (ester) and 1705 cm^{-1} (ketone and aldehyde); nmr δ 9.52 (t, 1H, J = 1.5 Hz, -CHO), 3.59 (s, 3H, $-COOCH_3$), 2.11 (s, 3H, $-COCH_3$), 1.07 (s, 6H, $-CH_3$); mass spectrum M^+ 198.1250 (Calcd. for $C_{11}H_{18}O_3$: 198.1255)] without purification was dissolved in 100 ml of benzene. To this solution

p-toluenesulfonic acid (2.58 g, 15 mmol) was added. The resulting mixture was refluxed for 5 hr with continous removal of water using a Dean-Stark water separator. After the solvent was removed _in vacuo_ ether was introduced to precipitate triphenylphosphine oxide. Filtration and concentration gave a residue which was subjected to bulb -to-bulb distillation at 100°C/2 torr. Enone ester _63_ (15.6 g, 70% yield) thus obtained showed the following physical data : $[\alpha]_D^{25}$ = -65.1° (c = 2.6, $CHCl_3$); ir 1675 (α,β-unsaturated ketone), 1735 (ester), 1380 and 1368 cm^{-1} (geminal methyls); nmr δ 6.75 (m, 1H, -COCH=C<u>H</u>-), 5.86 (dt, J = 10 Hz, J' = 2 Hz, 1H, -COC<u>H</u>=CH-), 3.61 (s, 3H, $-COOCH_3$), 1.11 (s, 3H, $-CH_3$) and 0.94 (s, 3H, $-CH_3$); mass spectrum M^+ 196.1095 (Calcd. for $C_{11}H_{16}O_3$: 196.1100).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found : C, 67.19; H, 8.40.

5-Carboxymethyl-6,6-dimethyl-2-cyclohexenone (_67_)

The keto ester _63_ (215 mg, 1.10 mmol) was dissolved in methanol (6 ml) and 2 N sodium hydroxide (3 ml) was added. The mixture was refluxed for 1.5 hr. After cooling to room temperature, it was diluted with water and washed with dichloromethane to remove the non-acidic meterial. Ice-cold hydrochloric acid was introduced to adjust the acidity of the solution to _ca_. pH 1. The resulting aqueous solution was extracted with dichloromethane. Combined extracts were dried ($MgSO_4$), filtered and concentrated to give acid _67_ (201 mg, quantitative yield) as an oil: $[\alpha]_D^{25}$ = -38.7° (c = 0.9, $CHCl_3$);

ir ($CHCl_3$) 3200-2500, 1708 (acid) and 1673 cm^{-1} (α,β-unsaturated ketone); nmr ($CDCl_3$) δ 10.65 (br. s, 1H, -COOH), 6.90 (m, 1H, -COCH=CH-), 5.00 (m, 1H, -COCH=CH-), 1.21 (s, 3H, $-CH_3$) and 1.04 (s, 3H, $-CH_3$); mass spectrum M^+ 182.0945 (Calcd. for $C_{10}H_{14}O_3$: 182.0943).

Vinyl (2',2'-dimethyl-3'-oxo-4'-cyclohexenyl)acetate (64)

The crude acid 67 (0.9 g) prepared from enone ester 63 (860 mg, 4.4 mmol) according to the procedure described in the proceeding experiment was dissolved in vinyl acetate (8 ml) and the solution was stirred for 30 min under a nitrogen atmosphere. Mercuric acetate (20 mg) and concentrated sulfuric acid (3 µl) were added. The reaction mixture was refluxed for 4 hr. Ice-cold aqueous sodium bicarbonate solution was added and the organic material extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate. Filtration and concentration yielded 819 mg of crude product which was chromatographed on silica gel (50 g). Elution with pentane-benzene (1:4) afforded pure ester 64 (610 mg, 67% yield) as an oil : ir 3080, 1642 (olefins), 1745 (ester), 1670 (α,β-unsaturated ketone), 1390 and 1370 cm^{-1} (geminal methyls); nmr δ 7.28 (dd, J = 14 Hz, J' = 6 Hz, 1H, -OCH=CH-), 6.80 (m, 1H, -COCH=CH-), 5.89 (dt, J = 10 Hz, J' = 2 Hz, 1H, -COCH=CH-), 4.83 (dd, J = 14 Hz, J' = 2 Hz, 1H, -OCH=CH-), 4.55 (dd, J = 6 Hz, J' = 2 Hz, 1H, -OCH=CH-), 1.12 (s, 3H, $-CH_3$) and 0.96 (s, 3H, $-CH_3$); mass spectrum M^+ 208.1109 (Calcd. for $C_{12}H_{16}O_3$: 208.1100).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found : C, 69.41,

H, 7.94.

Allyl (2',2'-dimethyl-3'-oxo-4'-cyclohexenyl)acetate (66)

The crude acid 67 prepared from enone ester 63 (370 mg, 1.9 mmol) was dissolved in acetone (8 ml). To this solution, anhydrous potassium carbonate (690 mg) was added. The resulting mixture was stirred at room temperature for 2 hr before allyl bromide (0.87 ml, 10 mmol) was introduced. After standing at reflux temperature for 5 hr, water was added and the aqueous solution was extracted with dichloromethane. Drying ($MgSO_4$), filtration and concentration gave the crude product which was purified by column chromatography on silica gel (30 g). Elution with benzene gave the allyl ester 66 (331 mg, 79% yield from 63) : ir 3030, 3010, 1660 (olefins), 1675 (α,β-unsaturated ketone) and 1735 cm^{-1} (ester); nmr δ 6.66 (m, 1H, -COCH=C$\underline{H}$-), 5.95 (m, 1H, -C$\underline{H}$=CH_2), 5.75 (m, 1H, -COC$\underline{H}$=CH-), 5.35 (m, 1H, -CH=C$\underline{H}$-), 5.15 (m, 1H, -CH=C$\underline{H}$-), 4.50 (m, 2H, -OC$\underline{H}_2$CH=CH-), 1.12 (s, 3H, -CH_3) and 0.95 (s, 3H, -CH_3); mass spectrum M^+ 222.1261 (Calcd. for $C_{13}H_{18}O_3$: 222.1256).

6,6-Dimethyl-5-(2'-hydroxyethyl)-2-cyclohexen-1-ol (69)

At 0°C, to a suspension of lithium aluminium hydride (228 mg, 6 mmol) in tetrahydrofuran (10 ml), was added a solution of the enone ester 63 (413 mg, 2.1 mmol) in tetrahydrofuran (2 ml) in one portion. After 15 min the reaction mixture was allowed to warm up to room temperature and stirred for 5 hr. The mixture was treated successive-

ly with 0.2 ml of water, 0.2 ml of 3 N sodium hydroxide solution and again with 0.6 ml of water. The inorganic salt was removed by filtration. Concentration of the filtrate gave diol 69 (257 mg, 72% yield) : ir ($CHCl_3$) 3340 (alcohol), 3020 and 1660 cm^{-1} (olefin); nmr ($CDCl_3$) δ 5.58 (m, 2H, -CH=CH-), 3.83 (br. s, 1H, >CHOH), 3.60 (m, 2H, $-CH_2OH$), 2.55 (br. s, 2H, -OH), 1.00 (s, 1H, $-CH_3$) and 0.70 (s, 1H, $-CH_3$); mass spectrum M^+ 170.1307 (Calcd. for $C_{10}H_{18}O_2$: 170.1307).

6,6-Dimethyl-5-(2'-oxoethyl)-2-cyclohexenone (70)

To a suspension of pyridinium chlorochromate (2.37 g, 11 mmol) in dichloromethane (26 ml), a solution of diol 69 (470 mg, 2.8 mmol) in dichloromethane (4 ml) was introduced in one portion. The mixture was stirred at room temperature for 2 hr and diluted with ether (50 ml). The resulting mixture was passed through a short pad of florisil. Removal of the solvent under the reduced pressure gave 70 (315 mg, 69% yield) : ir 2730, 1735 (aldehyde) and 1680 cm^{-1} (α,β-unsaturated ketone); nmr δ 9.70 (m, 1H, -CHO), 6.70 (m, 1H, -COCH=CH-), 5.83 (dt, J = 10 Hz, J' = 2 Hz, 1H, -COCH=CH-), 1.12 (s, 3H, $-CH_3$) and 0.96 (s, 3H, $-CH_3$); mass spectrum M^+ 166.0997 (Calcd. for $C_{10}H_{14}O_2$: 166.0994).

5-(2'-Acetoxy-3'-propenyl)-6,6-dimethyl-2-cyclohexenone (68)

At -78°C, to a stirred solution of keto aldehyde 70 (181 mg, 1.1 mmol) in tetrahydrofuran (5 ml) under a nitrogen atmosphere, was added a 1.2 M solution of vinyl magnesium bromide in tetrahydrofuran (1 ml,

1.2 mmol). After stirring for 30 min, ice-cold aqueous ammonium chloride solution was added. The resulting solution was extracted with ether. The etherate solution was dried ($MgSO_4$), filtered and evaporated to dryness to give crude keto alcohol 71 (200 mg) which was dissolved in pyridine (2 ml). To this solution, acetic anhydride (0.5 ml) was added. After stirring at room temperature for 16 hr, the reaction mixture was concentrated. The residue was chromatographed on silica gel. Elution with a solution of 2% ether in benzene afforded pure acetate 68 (126 mg, 50% yield) : ir 1735 (ester), 1675 (α,β-unsaturated ketone), 1395 and 1375 cm^{-1} (geminal methyls); nmr δ 6.68 (m, 1H, -COCH=CH-), 5.80 (dt, J = 10 Hz, J' = 3 Hz, 1H, -COCH=CH-), 5.58 (m, 1H, $-CH=CH_2$), 5.20 (m, 2H, $-CH=CH_2$), 5.16 (m, 1H, >CHOAc), 2.00, 1.98 (both s, total 3H, $-OCOCH_3$), 1.11, 1.08 and 0.94 (all s, total 6H, $-CH_3$); mass spectrum M^+ 236.1408 (Calcd. for $C_{14}H_{20}O_3$: 236.1413).

3-Acetoxy-9,9-dimethyltricyclo[$4.3.1.0^{4,7}$]decan-8-one (72a)

Enone acetate 68 (94 mg, 0.4 mmol) was dissolved in 10 ml of methanol. The solution was placed in a pyrex tube and irradiated at room temperature using a 450 W Hanovia high-pressure quartz mercury vapor lamp for 4 hr. The solution was concentrated and the residue chromatographed on silica gel (9 g). Elution with a solution of 2% ether in benzene gave keto acetate 72a (40 mg, 43% yield) as a colorless liquied : ir 1735 (ester), 1700 (ketone), 1390 and 1372 cm^{-1} (geminal methyls); nmr δ 4.84 (m, 1H, >CHOAc), 1.95 (s, 3H, $-OCOCH_3$), 1.21 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$); mass spectrum M^+ 236.1419

(Calcd. for $C_{14}H_{20}O_3$: 236.1412).

3-Hydroxy-9,9-dimethyltricyclo[4.3.1.0^{4,7}]deca-8-one (73)

Keto acetate 72a (170 mg, 0.72 mmol) was dissolved in 6 ml of methanol and saturated aqueous potassium carbonate (3 ml) was added. The reaction mixture was refluxed for 1.5 hr, poured into water and extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered and concentrated to yield an oily product (120 mg) which was chromatographed on silica gel (10 g). Elution with ether-benzene (3:2) gave 73 (91 mg, 65% yield) : ir 3400 (alcohol) and 1695 cm^{-1} (ketone); nmr δ 3.78 (m, 1H >CH-OH), 1.12 (s, 3H, $-CH_3$) and 0.98 (s, 3H, $-CH_3$).

9,9-Dimethyltricyclo[4.3.1.0^{4,7}]deca-3,8-dione (74)

At 0°C, to a solution of keto alcohol 73 (91 mg, 0.46 mmol) in acetone (5 ml) was added 8 N Jones reagent (0.3 ml) (52). After stirring at room temperature for 10 min, the mixture was diluted with water and extracted with ether. The organic solution was dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was chromatographed on silica gel (6 g). Elution with a solution of 2% ether in benzene gave 74 (70 mg, 80% yield) : ir 1695 and 1710 cm^{-1} (ketone); nmr δ 2.96 (d, J = 2.5 Hz, 2H, $-COCH_2-$), 1.13 (s, 3H, $-CH_3$) and 1.08 (s, 3H, $-CH_3$).

10,10-Dimethyl-4-oxatricyclo[$5.3.1.0^{5,8}$]deca-3,9-dione (75)

A mixture of the diketone 74 (80 mg, 0.4 mmol), m-chloroperbenzoic acid (259 mg, 1.2 mmol) and sodium bicarbonate (200 mg, 2.0 mmol) in dichloromethane (4 ml) was stirred for three days. A 10% aqueous sodium sulfite solution (5 ml) was added and the resulting solution was extracted with dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate solution. Concentration gave an oil which was chromatrographed on silica gel. Elution with a solution of 10% ether in benzene gave the keto lactone 75 (50 mg, 60% yield) : ir 1730 (lactone) and 1705 cm^{-1} (ketone); nmr δ 5.04 (m, 1H, >CHOCO-), 1.21 (s, 3H, $-CH_3$) and 1.11 (s, 3H, $-CH_3$); mass spectrum M^+ 208.1105 (Calcd. for $C_{12}H_{16}O_3$: 208.1100).

Cis-3-carbomethoxymethyl-2,2-dimethyl-5-(2'-oxoethyl)cyclohexanone (78)

The lactone 75 (20 mg, 0.1 mmol) was dissolved in 6 ml of methanol. To this solution, saturated aqueous potassium carbonate (3 ml) was added. The reaction mixture was refluxed for 30 min under a nitrogen atmosphere. After cooling to room temperature, it was poured into water and extracted with dichloromethane. Drying ($MgSO_4$), filtration and concentration yielded the acid 77 (10 mg, 45% yield): ir ($CHCl_3$) 3200-2500 (acid), 2730, 1705 (aldehyde) and 1705 cm^{-1} (ketone); nmr ($CDCl_3$) δ 11.8 (br. s, 1H, -COOH), 9.76 (br. s, 1H, -CHO), 1.11 (s, 3H, $-CH_3$) and 1.01 (s, 3H, $-CH_3$); mass spectrum M^+ 226.1207 (Calcd. for $C_{12}H_{18}O_4$: 226.1205).

The crude acid was dissolved in ether (4 ml). At 0°C, to this solution, diazomethane in ether was added dropwise until the light yellow color retained (<u>ca</u>. 1 ml). Removal of the solvent gave the ester <u>78</u> (10 mg, 95% yield): ir 2730, 1710 (aldehyde), 1735 (ester) and 1710 cm^{-1} (ketone); nmr δ 9.72 (s, 1H, -CHO), 3.62 (s, 3H, $-COOCH_3$), 1.15 (s, 3H, $-CH_3$) and 0.98 (s, 3H, $-CH_3$); mass spectrum M^+ 240.1362 (Calcd. for $C_{13}H_{20}O_4$: 240.1362).

<u>Photoaddition of enone 63 with vinyl acetate</u>

To a photochemical reaction vessel (53) containing enone ester <u>63</u> (2.15 g, 11 mmol) in benzene (50 ml), was added fresh distilled vinyl acetate (21 ml, 0.22 mol). The mixture was irradiated using a 450 W Havonia high-pressure quartz mercury lamp and a pyrex filter for 1.5 hr. The solution was concentrated and the residue chromatograped on silica gel (300 g) with benzene elution to give 2.37 g (77 % yield) of photoadducts <u>82</u> and <u>83</u> : ir 1735 (ester) and 1698 cm^{-1} (ketone); nmr δ 3.61 (s, 3H, $-COOCH_3$), 1.95, 1.96 (both s, total 3H, $-OCOCH_3$) and 0.9-1.1 (complex, 6 H, $-CH_3$); mass spectrum M^+ 282.1462 (Calcd. for $C_{15}H_{22}O_5$: 282.1467).

<u>4-Carbomethoxymethyl-7-hyxroxy-3,3-dimethylbicyclo[4.2.0]octan-2-one (85), cis-(78) and trans-3-carbomethoxymethyl-2,2-dimethyl-5-(2'-oxoethyl)cyclohexanone (84)</u>

At 0°C, sodium (690 mg, 30 g-atom) was added to methanol (35 ml). After all sodium reacted, a mixture of photoadducts <u>82</u> and <u>83</u> was

added. The resulting mixture, after stirring at room temperature for 45 min, was carefully poured into ice-cold 3 N hydrochloric acid (100 ml) and extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered and concentrated to give an oily residue which was chromatographed on silica gel (120 g). Elution with a solution of 50% ether-pentane gave keto aldehydes 78 and 84 (0.42 g, 16% yield) : ir 2730, 1710 (aldehyde), 1735 (ester) and 1710 cm^{-1} (ketone); mass spectrum M^+ 240.1355 (Calcd. for $C_{13}H_{20}O_4$: 340.1362); The nmr spectrum of the mixture showed, in addition to one set of signals corresponding to keto aldehyde 78 (*vide supra*), following signals for compound 84 : δ 9.72 (s, 1H, -CHO), 3.62 (s, 3H, $-COOCH_3$), 1.03 (s, 3H, $-CH_3$) and 0.98 (s, 3H, $-CH_3$).

Further elution with a solution of ether-pentane (4:1) gave alcohol 85 (1.75 g, 67% yield) : ir 3450 (alcohol), 1738 (ester) and 1702 cm^{-1} (ketone); nmr δ 3.60 (s, 3H, $-COOCH_3$), 3.76 (m, 1H, >CHOH) and 0.90-1.21 (six s, total 6H, $-CH_3$); mass spectrum M^+ 240.1355 (Calcd. for $C_{13}H_{20}O_4$: 240.1362).

4-Carbomethoxymethyl-3,3-dimethylbicyclo[4.2.0]octane-2,7-diones (86 and 87)

At 0°C, to a solution of diastereomeric alcohols 85 (3.2 g, 13.3 mmol) in acetone (30 ml), 8 N Jones reagent (*ca.* 5 ml) was introduced dropwise until the brown color persisted for more than 30 sec. The mixture was stirred at room temperature for 30 min. After most of the solvent was removed under the reduced pressure, water was added. The

resulting aqueous solution was extracted with chloroform. The extracts were washed successively with aqueous sodium bicarbonate and aqueous sodium chloride solution and dried ($MgSO_4$). Filtration and concentration yielded 2.6 g of crude product which showed two partially overlapping spots on silica gel thin-layer chromatography. Column chromatography on silica gel, eluted with a solution of 40% ether in pentane gave diketone 86 (850 mg, 27% yield): $[\alpha]_D^{25} = +119.5^\circ$ (c = 2.0, $CHCl_3$); ir 1785 (four-membered ketone), 1738 (ester) and 1710 cm^{-1} (ketone); nmr δ 3.61 (s, 3H, $-COOCH_3$), 1.21 (s, 3H, $-CH_3$) and 0.97 (s, 3H, $-CH_3$); mass spectrum M^+ 238.1204 (Calcd. for $C_{13}H_{18}O_4$: 238.1205).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found : C, 65.20; H, 7.28.

Further elution with the same solvent system gave 234 mg of a mixture of 86 and 87 (7% yield). This was followed by the pure ketone 87 (1.055 g, 33% yield) as a white solid : m.p. 127-128°C (ether); $[\alpha]_D^{25} = -126.3^\circ$ (c = 1.4, $CHCl_3$); ir ($CHCl_3$) 1785 (four-membered ketone), 1738 (ester) and 1708 cm^{-1} (ketone); nmr δ 3.67 (s, 3H, $-COOCH_3$), 1.12 (s, 3H, $-CH_3$) and 1.06 (s,3H, $-CH_3$); mass spectrum M^+ 238.1205 (Calcd. for $C_{13}H_{18}O_4$: 238.1205).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found : C, 65.79; H, 7.80,

4-Carbomethoxymethyl-7-hydroxy-3,3-dimethylbicyclo[4.2.0]octan-2-one (88)

To a solution of diketone 86 (129 mg, 0.5 mmol) in 8 ml of tetrahydrofuran, was added lithium aluminium tri-t-butoxyhydride (161 mg, 0.63 mmol). After stirring at 0°C for 1 hr, water (0.1 ml), 3 N sodium hydroxide (0.1 ml) and again water (0.3 ml) were successively added. Filtration followed by concentration of the resulting filtrate gave the crude product which was purified by column chromatography on silica gel. Elution with a solution of 30% ether in benzene gave alcohol 88 (82 mg, 68% yield) : ir 3450 (alcohol), 1735 (ester) and 1705 cm^{-1} (ketone); nmr δ 4.30 (t, J= 7 Hz, >CHOH), 3.68 (s, 3H, $-COOCH_3$), 1.11 (s, 3H, $-CH_3$) and 1.07 (s, 3H, $-CH_3$); mass spectrum M^+ 240.1358 (Calcd. for $C_{13}H_{20}O_4$: 240.1362).

4-Carbomethoxymethyl-7-hydroxy-3,3-dimethylbicyclo[4.2.0]octan-2-one (91)

To a solution of diketone 87 (68 mg, 0.28 mmol) in 5 ml of tetrahydrofuran, was added lithium aluminium tri-t-butoxyhydride (108 mg, 0.5 mmol). After stirring at 0°C for 1 hr, water (0.1 ml), 3 N sodium hydroxide (0.1 ml) and again water (0.3 ml) were successively introduced. Filtration followed by concentration of the filtrate gave the crude product which was purified by column chromatography on silica gel. Elution with a solution of 30% ether in benzene gave alcohol 91 (32 mg, 48% yield) : ir 3450 (alcohol), 1735 (ester) and 1695 cm^{-1}(ketone); nmr δ 4.32 (m, 1H, >CHOH), 3.67 (s, 3H, $-COOCH_3$), 1.16 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$); mass spectrum M^+ 240.1366 (Calcd. for $C_{13}H_{20}O_4$: 240.1362).

4-Carbomethoxymethyl-7,7-diethoxy-3,3-dimethylbicyclo[4.2.0]octan-2-one (92)

To a pyrex tube containing a solution of enone ester 63 (500 mg, 2.5 mmol) in benzene (12 ml), diethoxyketene (4.35 g, 37.5 mmol) was added. The reaction mixture was irradiated at room temperature with a 450 W Havonia high-pressure mercury lamp for 3 hr. The solvent and excess ketene were removed under the reduced pressure and the residue was chromatographed on silica gel (40 g). Elution with a solution of 20% ether in pentane gave a diastereomeric mixture of adducts 92 (750 mg, 96% yield) : ir 1735 (ester) and 1700 cm^{-1} (ketone); nmr δ 3.61 (s, 3H, $-COOCH_3$), 3.33, 3.39 (two q, J = 7 Hz, total 4H, $-OCH_2CH_3$) and ~1.10 (complex, total 12H, $-CH_3$); mass spectrum M^+ 312.1943 (Calcd. for $C_{17}H_{28}O_5$: 312.1937).

Diketones 86 and 87 from ketal 92

Ketal 92 (680 mg, 2.2 mmol) was dissolved in 8 ml of acetone and 2 N aqueous hydrochloric acid (4 ml) was added. After stirring at room temperature for 3 hr, the solution was diluted with water and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was chromatographed on silica gel (40 g). Elution with a solution of 40% ether in pentane gave pure diketones 86 (160 mg, 30% yield) and 87 (260 mg, 50% yield).

Mixture of $\Delta^{1,6}$- (94) and $\Delta^{1,8}$-4-carbomethoxymethyl-3,3-dimethylbicyclo [4.2.0] octene-2,7-dione (93)

To a solution of the diketone 87 (100 mg, 0.42 mmol) in 4 ml of glacial acetic acid, pyridinium bromide perbromide (268mg, 0.84 mmol) was added. The reaction mixture was stirred at room temperature overnight. It was cautiously made basic with ice-cold saturated aqueous sodium bicarbonate solution. Extraction with dichloromethane followed by the usual work-up of the extracts gave a thick oil which was chromatographed on silica gel (6 g). Elution with a solution of 25% ether in pentane gave enediones 93 and 94 (65 mg, 64% yield) : ir 1785 (four-membered ketone), 1740 (ester), and 1695 cm^{-1} (six-membered ketone); nmr δ 5.44 (br. s, 0.88H, -CH=C<), 3.65 (s, 3H, $-COOCH_3$), 3.42 (m, 0.24H, $-COCH_2C{=}C$), 1.22, 1.28 (2s, 3H, $-CH_3$) and 1.08 (s, 3H, $-CH_3$); mass spectrum M^+ 236.1048 (Calcd. for $C_{13}H_{16}O_4$:236.1049).

Reduction of enediones 93 and 94

Zinc dust (1 g, 0.015 g-atom) was added to a solution of enediones 93 and 94 (523 mg, 2.21 mmol) in 8 ml of glacial acetic acid. The resulting mixture was stirred at room temperature for 5 hr. It was then cautiously made basic with ice-cold saturated aqueous sodium bicarbonate solution. Extraction with dichloromethane followed by concentration of the organic solution gave an oily product which was chromatographed on silica gel (30 g). Elution with a solution of 40% ether in pentane afforded the isomeric ketones 86 (192 mg, 39% yield) and 87 (135 mg, 26% yield).

4-Carbomethoxymethyl-2,2,7,7-bisethylenedioxy-3,3-dimethylbicyclo [4.2.0]octane (95)

The diketone 86 (48 mg, 0.2 mmol) was dissolved in 10 ml of benzene. p-Toluenesulfonic acid (15 mg, 0.1 mmol) and ethylene glycol (0.5 ml) were added. The resulting solution was refluxed with constant removal of water using a Dean-Stark water separator for 24 hr. After cooling to room temperature, it was poured into ice-cold saturated sodium bicarbonate solution and extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was chromatographed on silica gel (10 g), eluted with a solution of 40% ether in pentane to afford diketal 95 (45 mg, 70% yield): ir 1735 cm^{-1} (ester); nmr δ 3.80 (m, 8H, $-OCH_2CH_2O-$), 3.60 (s, 3H, $-COOCH_3$), 0.89 (s, 3H, $-CH_3$) and 0.80 (s, 3H, $-CH_3$); mass spectrum M^+ 326.1723 (Calcd. for $C_{17}H_{26}O_6$: 326.1726).

4-Carbomethoxymethyl-7,7-ethylenedioxy-3,3-dimethylbicyclo[4.2.0]octan-2-one (96)

The diketone (655 mg, 2.76 mmol) was dissolved in 8 ml of 2-methyl-2-ethyl-1,3-dioxalane and p-toluenesulfonic acid (40 mg, 0.26 mmol) was added. The mixture was heated at 95°C (oil bath temperature) for 12 hr. After cooling to 0°C, aqueous sodium bicarbonate solution was added. Extraction with dichloromethane followed by the usual work-up of the extracts and chromatography of the crude product on silica gel (30 g), eluted with a solution of 40% ether in benzene,

gave ketal 96 (650 mg, 84% yield) : $[\alpha]_D^{25} = +71.8°$ (c = 1.5, $CHCl_3$); ir 1735 (ester) and 1715 cm^{-1} (ketone); nmr δ 3.75 (m, 4H, $-OCH_2CH_2O-$), 3.72 (s, 3H, $-COOCH_3$), 1.06 (s, 3H, $-CH_3$) and 0.96 (s, 3H, $-CH_3$); mass spectrum M^+ 282.1471 (Calad. for $C_{15}H_{22}O_5$: 282.1467).

4-Carbomethoxymethyl-7,7-ethylenedioxy-2-hydroxy-2,3,3-trimethylbicyclo[4.2.0]octane (98)

(A) To a solution of keto ester 96 (209 mg, 0.74 mmol) in methanol (6 ml) was added 2 N aqueous sodium hydroxide (3 ml). The resulting mixture was refluxed for 1 hr. After cooling to room temperature, the mixture was poured into ice-cold dilute hydrochloric acid and extracted with dichloromethane. The usual work-up of the extracts gave crude acid 97. The crude acid was then dissolved in 1,2-dimethoxyethane (10 ml) and cooled to 0°C. Sodium hydride (31 mg, 50% oil dispersion, 0.4 mmol) was added. After the evolution of gas ceased, a solution of 2 M methyl magnesium bromide in ether (1.8 ml, 3.6 mmol) was slowly introduced. The mixture was allowed to warm up to room temperature and stirred for 20 hr under a nitrogen atmosphere. Saturated aqueous ammonium chloride solution was added and the resulting mixture was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and concentrated to give acid 104 as a light yellow liquid. The crude acid was dissolved in 6 ml of ether and excess ethereal diazomethane was introduced. The residue obtained upon concentration was chromatographed on silica gel (20 g). Elution with a solution of 40% ether in pentane gave the starting

material 96 (39 mg, 19% recovery). Further elution with a solution of 50% ether in pentane afforded alcohol 98 (140 mg, 64% yield) as an oil : ir 3520 (alcohol) and 1735 cm^{-1} (ester); nmr δ 3.81 (br. s, 4H, $-OCH_2CH_2O-$), 3.63 (s, 3H, $-COOCH_3$), 1.10 (s, 3H, $-CH_3$), 0.96 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$); mass spectrum M^+ 298.1777 (Calcd. for $C_{16}H_{26}O_5$: 298.1780).

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found : C, 64.19; H, 8.68.

(B). Keto ester 96 (260 mg, 0.93 mmol) was dissolved in 6 ml of methanol and 2 N aqueous sodium hydroxide (3 ml) was added. The mixture was refluxed for 45 min. After cooling to $0^\circ C$, it was acidified with ice-cold dilute hydrochloric acid. Extraction with dichloromethane followed by the usual work-up of the organic solution, gave the oily acid 97 (240 mg). At $0^\circ C$, the crude acid was dissolved in ether (10 ml). A solution of 2 M methyl magnesium bromide in ether (3.4 ml, 6.8 mmol) was introduced dropwise. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 20 hr. Ice-cold ammonium chloride was added and the resulting mixture was made strongly acidic with dilute hydrochloric acid to approximately pH 2. Extraction with dichloromethane was followed by the usual work-up of the extracts. The crude product thus obtained was dissolved in ether. At $0^\circ C$, to this solution, was added ethereal diazomethane until the yellow color retained. Evaporation followed by column chromatography of the residue, using a solution of 40% ether in pentane as eluent, gave the starting material 96 (27 mg, 10%

recovery). Further elution with a solution of 50% ether in pentane gave hydroxy ester 98 (107 mg, 39% yield). Final elution with a solution of 80% ether in pentane afforded tertiary alcohol 99 (40 mg, 14% yield) : ir 3500 cm^{-1}(alcohol); nmr δ 3.86 (m, 4H, $-OCH_2CH_2O-$), 1.23 (s, 6H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 0.96 (s, 3H, $-CH_3$) and 0.89 (s, 3H, $-CH_3$); mass spectrum $(M-18)^+$ 280.2044 (Calcd. for $C_{17}H_{28}O_3$: 280.2038).

4-Carbomethoxymethyl-7,7-diethylenedioxy-3,3-dimethyl-2-methylidene bicyclo[4.2.0]octane (100)

To a solution of alcohol 98 (1.5 g, 5.0 mmol) in 4 ml of pyridine and 50 ml of benzene, was added a solution of thionyl chloride (1 ml) in 5 ml benzene. The mixture was stirred at room temperature under an atmosphere of nitrogen for 30 min. It was acidified with ice-cold 2 N aqueous hydrochloric acid and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Purification of the product was achieved by column chromatography on silica gel (80 g), eluted with a solution of 20% ether in pentane, to yield olefin 100 (1.176 g, 89% yield) : $[\alpha]_D^{25} = +41.4°$ (c = 1.0, $CHCl_3$); ir 3100, 1630, 890 (olefin) and 1740 cm^{-1} (ester); nmr δ 4.96 (br. s, 1H, >C=CH-), 4.78 (br. s, 1H, >C=CH-), 3.75 (br. s, 4H, $-OCH_2CH_2O-$), 3.60 (s, 3H, $-COOCH_3$), 1.10 (s, 3H, $-CH_3$) and 1.03 (s, 3H, $-CH_3$); mass spectrum M^+ 280.1674 (Calcd. for $C_{16}H_{24}O_4$: 280.1674).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found : C, 68.80; H, 8.69,

7,7-Ethylenedioxy-4-(2'-hydroxyethyl)-3,3-dimethyl-2-methylidene bicyclo[4.2.0]octane (102)

To a suspension of lithium aluminium hydride (200 mg, 5 mmol) in tetrahydrofuran at 0°C, a solution of ester 100 (1.176 g, 4.2 mmol) in tetrahydrofuran (2 ml) was added. The reaction mixture was stirred at room temperature overnight. Water (0.2 ml), 3 N sodium hydroxide (0.2 ml) and again water (0.6 ml) were successively added. Filtration followed by concentration of the filtrate gave 1.05 g of alcohol 102 as an oil : $[\alpha]_D^{25} = +39.2°$ (c = 1.3, $CHCl_3$); ir 3420 (alcohol), 3100 and 1630 cm^{-1} (olefin); nmr δ 4.91 (s, 1H, >C=CH-), 4.72 (s, 1H, >C=CH-), 3.74 (br. s, 4H, $-OCH_2CH_2O-$), 1.06 (s, 3H, $-CH_3$) and 1.03 (s, 3H, $-CH_3$); mass spectrum M^+ 252.1730 (Calcd. for $C_{15}H_{24}O_3$: 252.1725);

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 71.70; H, 9.66.

4-(2'-Chloroethyl)-7,7-ethylenedioxy-3,3-dimethyl-2-methylidenebicyclo [4.2.0]octane (103)

The alcohol 102 (190 mg, 0.75 mmol) was dissolved in 2 ml of pyridine and cooled to 0°C. Phosphorus oxychloride (0.5 ml) was introduced. The mixture was stirred at room temperature under a

nitrogen atmosphere for 16 hr and poured into ice-cold water. The resulting mixture was extracted with dichloromethane. The dichloromethane solution was dried ($MgSO_4$), filtered and evaporated to give an oily residue which was chromatographed on silica gel (15 g). Elution with a solution of 10% ether in pentane yielded ketal chloride 103 (150 mg, 75% yield) : $[\alpha]_D^{25} = +29.7^\circ$ (c = 0.7, $CHCl_3$); ir 1630 cm^{-1} (olefin); nmr δ 4.92 (s, 1H, >C=CH-), 4.75 (s, 1H, >C=CH-), 4.74 (br. s, 4H, $-OCH_2CH_2O-$), 3.50 (m, 2H, $-CH_2Cl$), 1.07 (s, 3H, $-CH_3$) and 1.03 (s, 3H, $-CH_3$); mass spectrum M^+ 270.1380 and 272.1362 (Calcd. for $C_{15}H_{23}OCl$: 270.1386 and 272.1357).

4-(2'-Chloroethyl)-3,3-dimethyl-2-methylidenebicyclo[4.2.0]octan-7-one (106)

The ketal chloride 103 (120 mg, 0.44 mmol) was dissolved in 4 ml of acetone and 2 N aqueous hydrochloric acid (2 ml) was added. After stirring at room temperature for 8 hr, the mixture was poured into water and extracted with dichloromethane. Drying ($MgSO_4$), filtration and concentration gave ketone 106 (100 mg, quantitative yield) : $[\alpha]_D^{25} = +48.6^\circ$ (c = 1.3, $CHCl_3$); ir 1785 (four-membered ketone) and 1640 cm^{-1} (olefin); nmr δ 5.04 (d, J = 2 Hz, 1H, >C=CH-), 4.91 (d, J = 2 Hz, >C=CH-), 3.50 (m, 2H, $-CH_2Cl$), 1.16 (s, 3H, $-CH_3$) and 1.11 (s, 3H, $-CH_3$); mass spectrum M^+ 226.1124 and 228.1090 (Calcd. for $C_{13}H_{19}OCl$: 226.1124 and 228.1095).

8-Carbethoxy-4-(2'-chloroethyl)-3,3-dimethyl-2-methylidenebicyclo [4.3.0]nonan-7-one (107) and 7-carbethoxy-4-(2'-chloroethyl)-3,3-dimethyl-2-methylidenebicyclo[4.3.0]nonan-8-one (108)

At 0°C, to a solution of keto chloride 106 (100 mg, 0.46 mmol) in 8 ml of ether, was added boron trifluoride etherate (0.12 ml, 1 mmol). After stirring at 0°C for 15 min, ethyl diazoacetate (0.1 ml, 1 mmol) was introduced. The mixture was stirred under a nitrogen atmosphere at 0°C for 1 hr and at room temperature for 4 hr. Ice-cold saturated aqueous sodium bicarbonate solution was added dropwise. Extraction with dichloromethane followed by the usual work-up of the organic solution gave an oily product which showed two spots in thin-layer chromatography. Their separation was effected by column chromatography on silica gel. Elution with a solution of 8% ether in pentane afforded the keto ester 107 (82 mg, 57% yield) : $[\alpha]_D^{25} = +31.9°$ (c = 0.6, $CHCl_3$); ir 1735 (ester), 1760 (five-membered ketone) and 1650 cm^{-1} (olefin); nmr δ 4.90 (br. s, 2H, $>C{=}CH_2$), 4.12 (q, J = 7 Hz, 2H, $-COOC\underline{H}_2CH_3$), 3.54 (m, 2H, $-CH_2Cl$), 1.24 (s, 3H, $-CH_3$), 1.23 (t, J = 7 Hz, 3H, $-COOCH_2C\underline{H}_3$) and 1.06 (s, 3H, $-CH_3$); mass spectrum M^+ 312.1490 and 314.1445 (Calcd. for $C_{17}H_{25}O_3Cl$: 312.1492 and 314.1462).

Further elution with the same solvent system gave keto ester 108 (42 mg, 29% yield) : ir 1730 (ester), 1750 (five-membered ketone) and 1635 cm^{-1} (olefin); nmr δ 4.98 (s, 1H, $>C{=}CH-$), 4.72 (s, 1H, $>C{=}CH-$), 4.14 (q, J = 7 Hz, 2H, $-COOC\underline{H}_2CH_3$), 3.52 (m, 2H, $-CH_2Cl$), 1.25 (t, J = 7 Hz, 3H, $-COOCH_2C\underline{H}_3$), 1.15 (s, 3H, $-CH_3$) and 1.01 (s, 3H, $-CH_3$); mass spectrum M^+ 312.1488 and 314.1466 (Calcd. for

$C_{17}H_{25}O_3Cl$: 312.1492 and 314.1463).

(-)-Khusimone (16)

To a solution of the keto ester 107 (122 mg, 0.36 mmol) in 3 ml of methanol, was added a 2 N sodium hydroxide solution (1.5 ml). The resulting solution was immediately brought into reflux using a pre-heated oil bath. After 40 min, ice-cold water was added. Extraction with dichloromethane, drying ($MgSO_4$), filtration and concentration gave a solid which was recrystalized from pet ether to give (-)-khusimone (16) (56 mg, 56% yield) : m.p. 78°C; $[\alpha]_D^{25}$ = -108.7° (c = 2.0, $CHCl_3$); ir ($CHCl_3$) 3140, 1640 (olefin), 1728 (five-membered ketone), 1395 and 1360 cm^{-1} (geminal methyls); nmr ($CDCl_3$) δ 4.84 (br.s, 1H, >C=CH-), 4.68 (br. s, 1H, >C=CH-) and 1.06 (s, 6H, two $-CH_3$); mass specetum M^+ 204.1514 (Calcd. for $C_{14}H_{20}O$: 204.1512).

2,12-Epoxyzizaene (112)

At 0°C, to a suspension of trimethylsulfonium iodide (100 mg, 0.5 mmol) in 6 ml of tetrahydrofuran under a nitrogen atmosphere, was added a soltuion of 2 M butyl lithium in ether (0.16 ml, 0.32 mmol). After stirring at room temperature for 1 hr, the mixture was again cooled to 0°C and a solution of ketone 16 (40 mg, 0.2 mmol) in tetrahydrofuran (4 ml) was added. The resulting mixture was stirred at room temperature for 2.5 hr. Water was added and the aqueous solution extracted with dichloromethane. The usual work-up of the extracts gave an oil which was chromatographed on silica gel column

(6 g). Elution with a solution of 2% ether in pentane gave epoxide 112 (15 mg, 51% based on consumed starting material) : ir 3110 and 1645 (olefin), 1385 and 1365 cm^{-1} (geminal methyls); nmr δ 4.77 (m, 1H, >C=CH-), 4.58 (br. s, 1H, >C=CH-), 2.67 (d., J = 12 Hz, 1H, $>\overset{O}{\widehat{C-C}}$-H), 2.53 (d, J = 12 Hz, 1H, $>\overset{O}{\widehat{C-C}}$-H) and 1.06 (s, 6H, two $-CH_3$); mass spectrum M^+ 218.1674 (Calcd. for $C_{15}H_{22}O$: 218.1670).

Further elution with a solution of 5% ether in pentane afforded 13 mg of the starting material.

Epizizaene-12-carboaldehyde (113)

The epoxide 112 (17.5 mg, 0.08 mmol) was dissolved in 4 ml of ether and cooled to 0°C. Boron trifluoride etherate (0.05 ml) was introduced. The mixture was stirred under a nitrogen atmosphere at 0°C for 1 hr, and then at room temperature for 30 min. It was made basic with saturated sodium bicarbonate and extracted with ether. The organic solution was dried ($MgSO_4$), filtered and concentrated to give aldehyde 113 (17.5 mg, quantitative yield) as an oil : ir 2710, 1720 (aldehyde), 1640 (olefin), 1380 and 1360 cm^{-1} (geminal methyls); nmr δ 9.73 (d, J = 2 Hz, 1H, -CHO), 4.80 (s, 1H, >C=CH-), 4.60 (s, 1H, >C=CH-), 1.10 (s, 3H, $-CH_3$) and 1.06 (s, 3H, $-CH_3$); mass spectrum M^+ 218.1670 (Calcd. for $C_{15}H_{22}O$: 218.1670).

(-)-Epizizanoic acid (14)

At 0°C, to a solution of the aldehyde 113 (16 mg, 0.08 mmol) in acetone (3 ml), was slowly added 8 N Jones reagent (*ca.* 0.5 ml) until

a brown color persisted. The mixture was stirred for 5 min, added to 50 ml of ice-cold aqueous sodium chloride solution and extracted with dichloromethane. The usual work-up of the extracts gave the crude product which was taken up in ether and extracted with saturated sodium bicarbonate. The extracts were combined and acidified with hydrochloric acid. This was followed by extraction with dichloromethane. Drying ($MgSO_4$), filtration and concentration gave (−)-epizizanoic acid (14) (13 mg, 77% yield) : m.p. 110°C (pet. ether); $[\alpha]_D^{25} = -1.0°$ (c = 1.2, $CHCl_3$); ir ($CHCl_3$) 3200-2500 (acid), 1691 (acid carbonyl), 1638 (olefin), 1380 and 1360 cm^{-1} (geminal methyls); nmr δ 11.7 (m, 1H, −COOH), 4.75 (s, 1H, >C=CH−), 4.56 (s, 1H, >C=CH−), 1.08 (s, 3H, $-CH_3$) and 1.05 (s, 3H, $-CH_3$); mass spectrum M^+ 234.1626 (Calcd. for $C_{15}H_{22}O_2$: 234.1619).

Epimerization of aldehyde 113

To a solution of aldehyde 113 (13 mg, 0.06 mmol) in 4 ml of methanol was added 2 N aqueous sodium hydroxide solution (1 ml). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 9 hr. Saturated sodium chloride was added and the resulting aqueous solution was extracted with dichloromethane. Drying ($MgSO_4$), filtration and evaporation of the solvent gave a mixture of epimeric aldehyde 113 and 114 which was separated by column chromatography. Elution with a solution of 5% ether in pet ether gave the pure β-aldehyde 114 (2.5 mg), an 1:1 mixture of α and β epimer (2 mg), followed by the pure α-aldehyde 113 (1.6 mg). The

β-aldehyde 114 showed the followed spectral data : ir 2720, 1720 (aldehyde), 1640 (olefin), 1380 and 1360 cm^{-1} (geminal methyls); nmr δ 9.80 (d, J = 2 Hz, 1H, -CHO), 4.78 (t, J= 2 Hz, 1H, >C=CH-), 4.63 (t, J = 2 Hz, 1H, >C=CH-) and 1.07 (s, 6H, two $-CH_3$); mass spectrum M^+ 218.1667 (Calcd. for $C_{15}H_{22}O$: 218.1670).

(+)- Zizanoic acid (9)

At 0°C, to a solution of aldehyde 114 (2.5 mg, 0.012 mmol) in 2 ml of acetone, was added 8 N Jones reagent (3 drops). After stirring at room temperature for 15 min, the reaction mixture was added to water and extracted with dichloromethane. The usual work-up of the extracts gave (+)-zizanoic acid (9) (2.3 mg, 90% yield) which showed a specific rotation of $[\alpha]_D^{25} = +22.2°$ (c = 0.23, $CHCl_3$); and spectral properties identical with those of natural product as follows : ir ($CHCl_3$) 3200-2600 (acid), 1701 (acid carbonyl) , 1639 and 891 cm^{-1} (olefin); nmr δ 4.77 (t, J = 1.5 Hz, 1H, >C=CH-), 4.63 (t, J = 1.5 Hz, 1H, >C=CH-), 2.68 (m, 1H, >CHCOOH), 1.10 (s, 3H, $-CH_3$) and 1.07 (s, 3H, $-CH_3$); mass spectrum M^+ 234.1621 (Calcd. for $C_{15}H_{22}O_2$: 234.1620).

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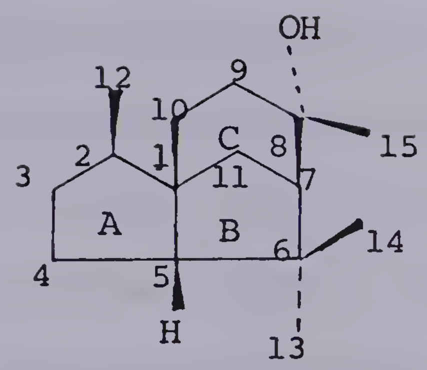
PART 2. SYNTHETIC STUDIES ON CEDRENOID SESQUITERPENES

INTRODUCTION

(+)-Cedrol (1), (−)- α-cedrene (2) and (+)-β-cedrene (3) are members of a small sesquiterpene family. The discovery of these tricyclic compounds dates back to 1841 when Walter (1) first observed their presence in cedar wood oil, the essential oil of several juniper species. The structure of these natural products had puzzled chemists for more than a century (2) until 1953 when two research groups (3,4) independently and correctly proposed their gross structures as depicted in formulas 1 - 3. Two years later, the structural assignments were confirmed and the relative stereochemistry determined by a total synthesis of (+)-cedrol (1) (5). By correlation of the absolute configuration of cedrene with that of α- and γ-patchoulene, Büchi and coworkers successfully established the absolute stereochemistry of the molecules (6).

Extensive attention has been drawn to the synthesis of cedrenoid sesquiterpenes. During the past two decades or so, no less than ten total syntheses (5, 7-15) have been documented . The first of these syntheses, which was executed with excellent stereochemical control, was accomplished by Stork and Clarke (5) who applied consecutive intramolecular condensation reactions for the construction of the tricyclic system. In their synthesis, ring A was introduced by an aldol process (4→5) and the condensation of keto ester 6, at a later stage, resulted in the formation of diketone 7 possessing the required ring skeleton.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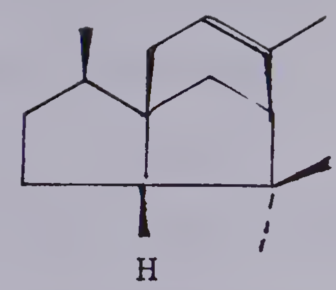
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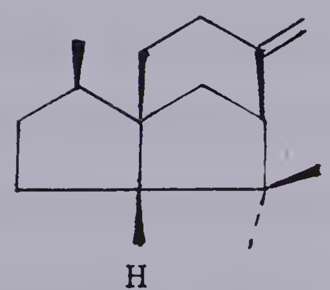
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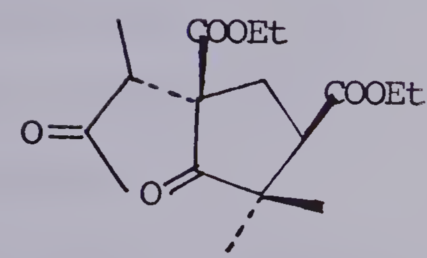
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COOEt
O
O

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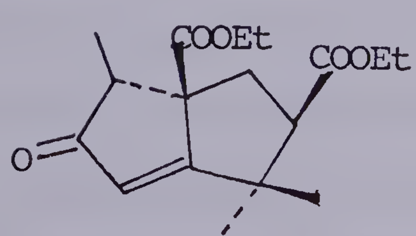
COOEt
COOEt
O

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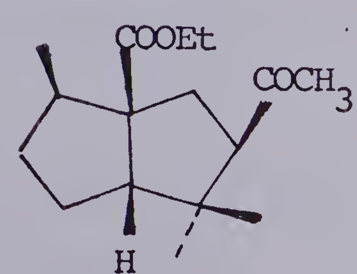
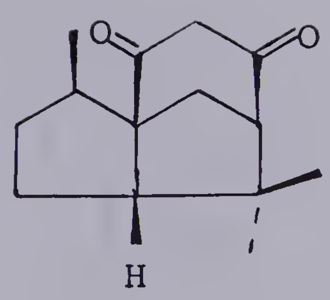

COOEt
$COCH_3$
H

6

Several subsequent syntheses (7-14) made use of various versions of polyene cyclization mimicking the biogenetic hypothesis (17) which is outlined in Scheme 1. In their first synthesis, Corey et al. successfully induced cyclization of diene 8 to tricyclic ketone 9 with boron trifluoride (7). A similar approach was independently applied by Crandall and Lawton (8) who found that unsaturated alcohol 10 underwent ring closure upon treatment with formic acid to give racemic α-cedrene (2). The cationic cyclization of spiro[5,4]decane derivatives was further expanded by Demole and coworkers (9). In their synthesis of α-cedrene, β-acoratriene (11) readily prepared from nerolidol (12) in four steps was converted to dehydro-α-cedrene (13) under the influence of boron trifluoride. A year later, an alternative route leading to β-acoratriene (11) was described (10).

A remarkably simplified transformation of nerolidol (12) to α-cedrene (2) was developed by Andersen and Syrdal (11) involving sequential treatment of the former compound with formic acid and trifluoroacetic acid without the isolation of the intermediate (s). Similarly, α-cedrene (2) was formed along with four other cyclization products when farnesol (14) was subjected to the treatment with boron trifluoride (12).

The second synthesis by Corey's group (13) involves, as the key step, a synchronous double annulation process whereby cyclopropyl ketone 15, when treated with ten equivalents of acetyl methanesulfonate, was transformed directly to ketone 9.



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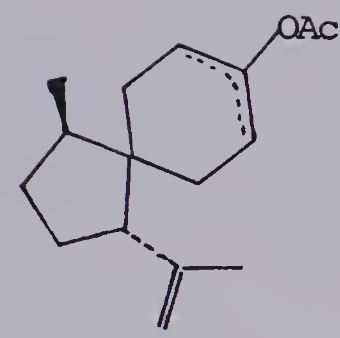

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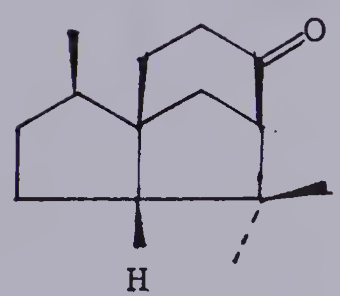

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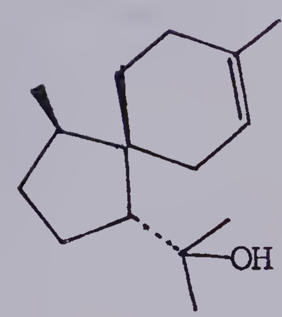

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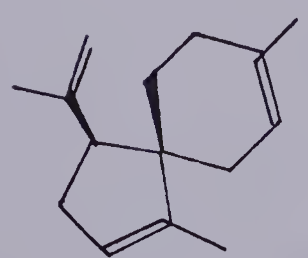

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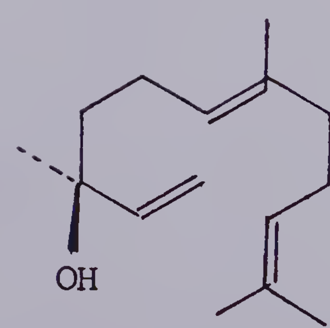

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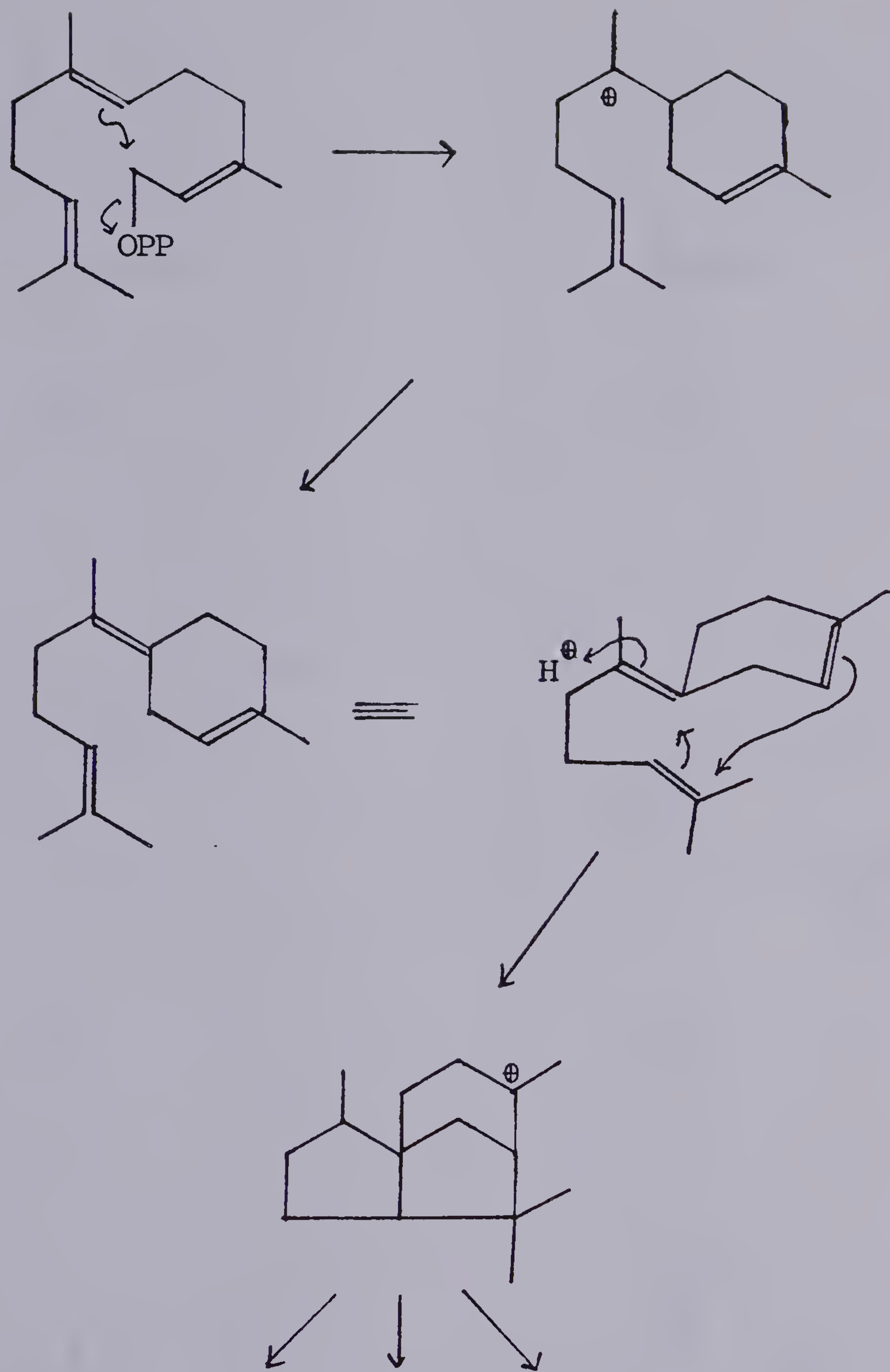
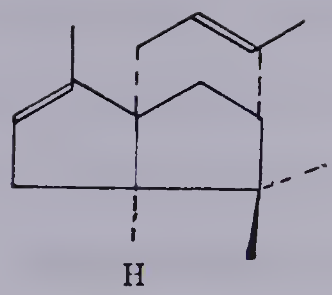


1 2 3

Scheme 1



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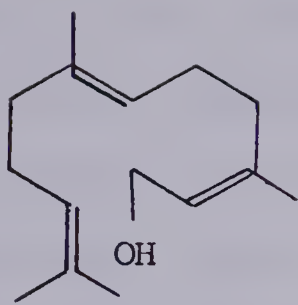

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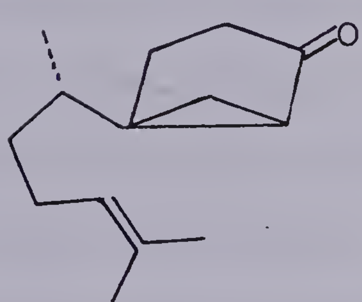

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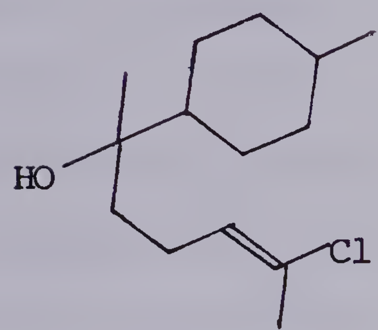

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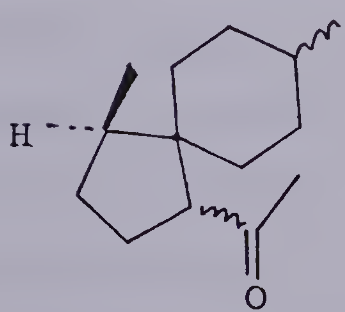

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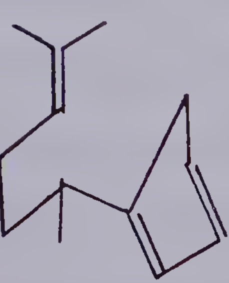

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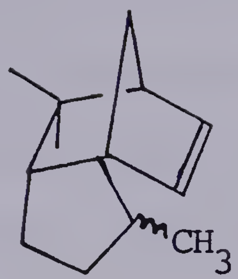
Lansbury and coworkers effectively applied their chloroalkene-annulation procedure to a cedrenoid synthesis (14). Thus, upon treatment with formic acid and acetic anhydride, hydroxy chloride 16 underwent cyclization to give ketone 17 which was subsequently modified to alcohol 10 whose cyclization to α-cedrene (2) had previously been demonstrated by Crandall and Lawton (*vide supra*).

A fundamentally different approach to cedrenoid synthesis has been developed by Fallis and Breitholle (15) utilizing an intramolecular Diels-Alder reaction which effected the cyclization of triene 18 to the key intermediate 19. More recently, another Canadian group (16) showed that diketone 20 underwent ring fission upon treatment with sodium methoxide in methanol under kinetically controlled conditions to give enone 21 possessing the cedrene ring skeleton. The transformation of the latter compound to the natural products remains however to be executed.

A conceivable synthetic route leading to cedrenoid sesquiterpenes involves trione 22 as a potential precursor. By a suitable acid/base treatment, it could, in principle, undergo consecutive intramolecular aldol condensation (22→23) and Michael addition (23→24) resulting in the formation of diketone 24 possessing the required tricyclic skeleton as well as adequate functionalities for further modifications. This approach constitutes the backbone of our studies on the total synthesis of cedrenoid sesquiterpenes. Present results are described in the second part of this thesis.



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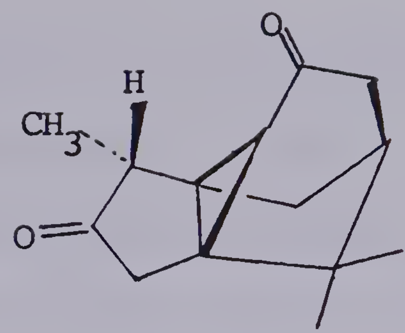

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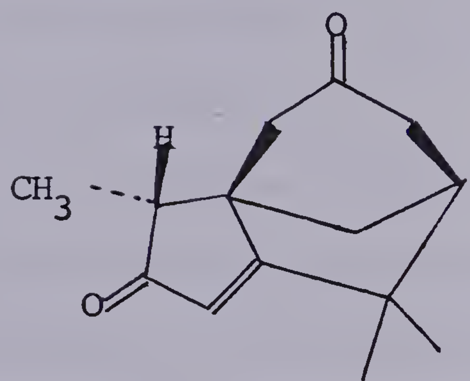

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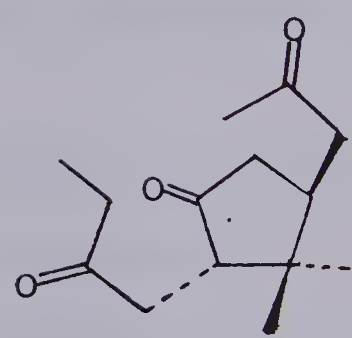

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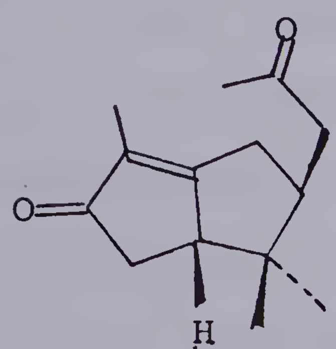

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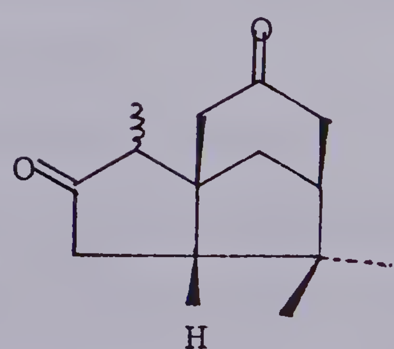

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RESULTS AND DISCUSSION

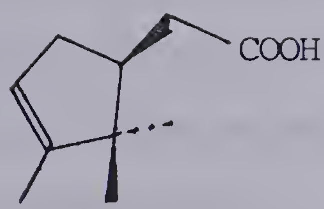
In part 1 of this thesis, the preparation of (-)-α-campholenic acid (25) by the reaction of commercially available (-)-ℓ-10-camphorsulfonic acid ammonium salt and fused potassium hydroxide was described. This carboxylic acid, which has the same chirality as the naturally occurring cedrenoid sesquiterpenes at C-7, appears to be an attractive starting material for the preparation of trione 22 (our immediate synthetic target) as it possesses not only a gem-dimethyl group and a substitution pattern similar to those found in the latter compound but also functionalities suitable for further modifications.

The transformation of (-)-α-campholenic acid (25) to trione 22 requires three primary operations: the extension of the carboxymethyl chain by one-carbon unit, the modification of the double bond to a ketonic function, and the incorporation of a propionyl group to its allylic methyl carbon. The former was accomplished by treatment of (-)-α-campholenic acid (25) with two equivalents of methyl lithium (18), which resulted in the formation of enone 26 in virtually quantitative yield.

Photo-oxygenation of enone 26 using methylene blue as a sensitizer followed by a reductive work-up using triethylphosphite (19) gave rise to a 66% yield of a mixture of two epimeric alcohols 27 which showed, in the ir spectrum, characteristic absorption bands at 3450 (hydroxy), 3100, 1665 (double bond), and 1715 cm^{-1} (ketone). The ratio of these two epimers was approximately 8:1

as determined by the nmr spectrum which displayed two pairs of methyl singlets with the major at δ 1.12 and 0.82 and the minor at δ 1.05 and 0.92. In agreement with the structural assignment, two broad singlets at δ 5.09 and 4.88 for the two vinylic protons as well as a methyl singlet at δ 2.12 were also observed. These two alcohols were found to be rather unstable and an attempted separation by column chromatography resulted in substantial loss of material. Since the newly introduced asymmetric center was to be destroyed in the subsequent transformation, their separation was in fact unnecessary. Oxidation of alcohols 27 with active manganese dioxide (20) in benzene afforded an 80% yield of enone 28 which showed, in the mass spectrum, a molecular ion peak at 180.1150 consistent with a molecular formula of $C_{11}H_{16}O_2$. Thus, by a two-step sequence the double bond was converted to the required cyclopentanone carbonyl with the allylic methyl group properly activated for the introduction of a propionyl moiety which was effected as follows, using a route developed by McMurry and coworkers for 1,4-diketone synthesis (21).

In the presence of potassium carbonate, enone 28 reacted smoothly with nitropropane in hot methanol to give nitro ketone 29 m.p. 81-2°C (ether-pet. ether), in 78% yield. The sharp melting point coupled with the simplicity of the nmr spectrum, which showed three singlets at δ 2.11, 1.05 and 0.61 and a triplet at δ 0.99 with a coupling constant of 7 Hz for a total of four methyl groups were suggestive of a single stereoisomer of 29.



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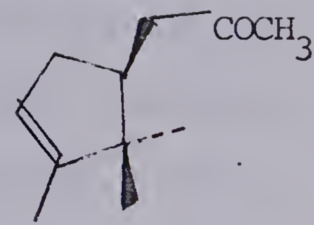

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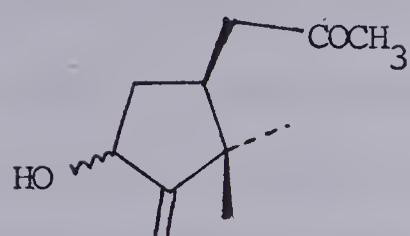

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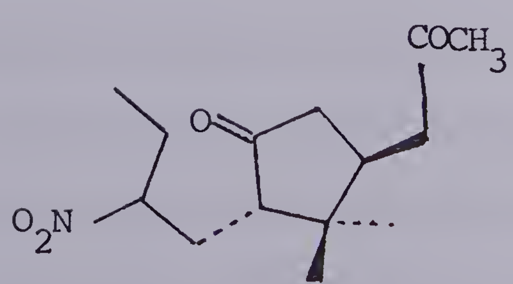


29

(23)

Since the conditions employed were expected to induce isomerization to give predominantly the thermodynamically more stable product, its stereochemistry was tentatively assigned as depicted. Subsequent treatment of the salt derived from nitro ketone 29 and one equivalent of sodium methoxide in methanol with ozone gave rise to the desired trione 22, m.p. 64-5°C (ether-pet. ether), in 74% yield. Its structure was readily established spectroscopically. The nmr spectrum displayed four methyl signals, three as sharp singlets at δ 2.12, 1.05 and 0.61 and the other as a triplet at δ 1.05 with a coupling constant 7 Hz. In the ir spectrum, diagnostic ketone carbonyl absorption bands were observed at 1735 and 1715 cm^{-1}. Exact mass measurement revealed a molecular weight of 238.1557 in agreement with the required formula of $C_{14}H_{22}O_3$. At this point, it was gratifying to realize that the optically active trione 22 could be obtained in a crystalline form and in a yield of ca. 25% from (-)-α-campholenic acid (25) by a five step reaction sequence.

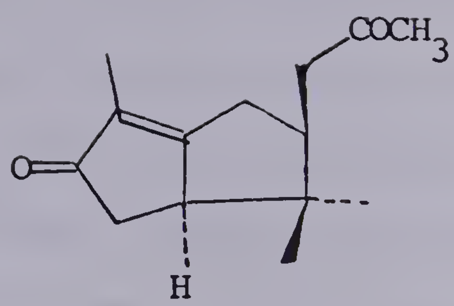
Our original synthetic plan called for two consecutive intramolecular cyclizations of trione 22, an aldol condensation for ring A formation followed by a Michael addition for that of ring C, to create the tricyclic ring skeleton of cedrenoid sesquiterpenes. Towards this end, trione 22 was subjected to treatment with sodium methoxide in refluxing methanol. After 24 hr, the reaction was found to be complete and a product was isolated in a yield of 95%. It was somewhat disappointing, however, to find that the

product was the bicyclic enone 30 as clearly defined by the ir spectrum which showed absorption bands at 1700 and 1660 cm^{-1} for the ketone carbonyl groups and the double bond respectively, and by the nmr spectrum in which the vinylic methyl appeared as a broad singlet at δ 1.60 and the methyl ketone group was observed at δ 2.13 as singlet, and by exact mass measurement which revealed its molecular weight as 220.1459 and hence a molecular formula of $C_{14}H_{20}O_2$. The nmr spectrum which also showed two singlets at δ 1.07 and 0.48 for the geminal dimethyls was further indicative of a single stereoisomer for the product. This was confirmed by ^{13}C nmr which displayed only fourteen signals. Its tentative stereochemical assignment was based on the consideration that the reaction conditions were sufficient to induce the epimerization of the enolizable chiral center to give stereoisomer 30 which was expected to be more stable than the alternative structure of 31 because of the exo orientation of its ketone side chain. The interruption of the anticipated cyclization process at the bicyclic stage could be attributed to the inadequacy of the reaction conditions and considerable efforts were made to attempt to bring about the desired ring closure. Unfortunately, prolonged treatment of enone 30 with sodium methoxide in refluxing methanol or with p-toluenesulfonic acid in benzene resulted in complete recovery of the starting material and 30 gave a complex mixture without apparent production of the tricyclic compound 24, when heated with potassium t-butoxide in t-butanol

at elevated temperature.

Conceptually, the synthesis of cedrenoid sesquiterpenes from enone 30 could be carried out by 1,4-addition of a functionalized ethyl group (30→32) followed by cyclization (32→33) and further modification of functionalities including a selective Baeyer-Villiger reaction (33→34). As a result of the above negative findings, this alternative approach was explored.

Two methods were employed for the incorporation of a functionalized ethyl group into enone 30. In the first instance, its saturated ketone carbonyl was first protected by the means of selective ketalization which was carried out using standard ketalization conditions (p-toluenesulfonic acid and ethylene glycol in refluxing benzene). The ^{13}C nmr of the product 35, which displayed sixteen carbon signals, was indicative of its homogeneity. When treated with acetone and p-toluenesulfonic acid under mild conditions, ketal 35 underwent transketalization giving rise to the starting enone 30. It was also found that ketal 35 was recovered intact after prolonged treatment with sodium methoxide in refluxing methanol. These results suggested that no isomerization occurred during the ketalization process and that ketal 35 was again the thermodynamically more stable stereoisomer. Ketal 35 was subsequently treated with lithium divinylcopper generated from vinyl lithium and cuprous bromide-methyl sulfide complex (22). The 1,4-addition proceeded rather smoothly to give a mixture of two inseparable epimeric ketones



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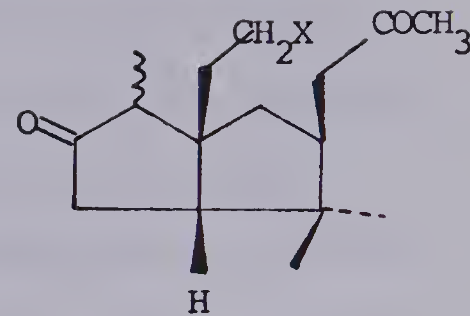

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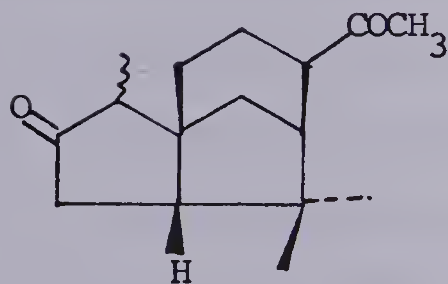

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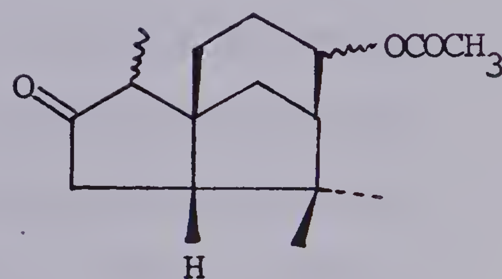

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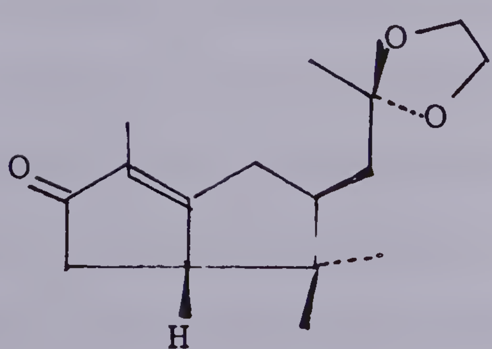

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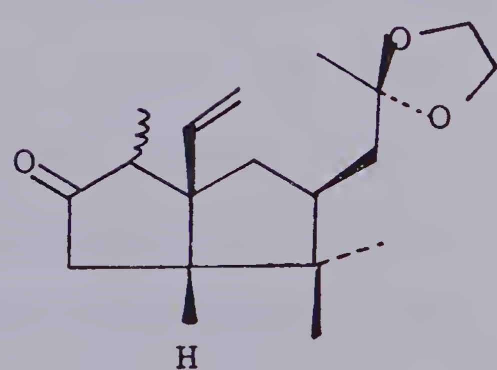

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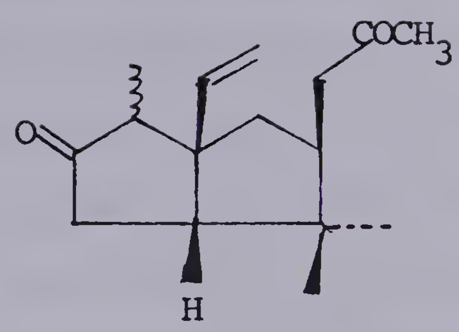
36 in 65% yield and in a ratio of 1;1. The cis stereochemistry assigned to its ring junction was precedented by ample examples (23-27) which showed that the 1,4-addition of organo "ate" complexes to enones took place preferentially from the sterically less hindered side. Removal of the ketal protecting group was effected by transketalization with acetone in the presence of p-toluenesulfonic acid as a catalyst. The resulting diketones 37 were epoxidized using m-chloroperbenzoic acid to give a mixture of diastereomeric epoxides 38 which were not separable. Having a functionalized two-carbon unit properly installed, the intramolecular displacement reaction to link the two side chains was attempted. Treatment of the mixture of epoxides 38 with sodium hydride in 1,2-dimethoxyethane at room temperature resulted in the total consumption of the starting material within a period of 12 hr. The excitement, however, soon vanished as the product which was obtained in a yield of 72%, was shown by the following spectral evidence to be a 1:1 mixture of two epimeric cyclopropyl ketones 39 isomeric with the desired compound 40. In the nmr spectrum, two sets of methyl singlets, one at δ 2.13, 1.09, 0.94 and 0.48, and the other at δ 2.13, 1.00, 0.90 and 0.40, as well as a two-proton multiplet at δ 3.60 diagnostic for the methylene group bearing the hydroxyl moiety were observed. The ir spectrum showed hydroxyl absorption at 3440 cm^{-1} and a single absorption band in the carbonyl region at 1712 cm^{-1} consistent only with structure 39. The structural assignment was further confirmed by the mass spectrum which displayed a

molecular ion peak at 264.1730. Although disappointing, the exclusive production of cyclopropyl ketone 39 was not totally unexpected and could be rationalized by invoking the faster formation of a three-membered ring than that of a six-membered one (28,29). In order to eliminate this problem, the following alternative route was investigated.

Irradiation of enone 30 with an excess of allene in tetrahydrofuran at -78°C resulted in the formation, in a yield of 81%, of photoadduct 41, apparently a single stereoisomer as revealed by the nmr spectrum showing only one set of four sharp methyl singlets at δ 2.06, 1.08, 0.90 and 0.32. Its orientation was readily assigned on the basis of the previous observations that the photocyclodddition of enones to allene proceeded in a head-to head manner (30,31) and confirmed by the subsequent transformations. With respect to the stereochemistry of enone photocycloadditions in general, it has been postulated (32) that the controlling factor is the preferential configuration of the excited state which is assumed to have carbonium ion character at α-carbon of the carbonyl group and an orbital with an electron pair at the β-carbon. In the present case, the stable configuration of such an excited state would be the one shown in formula 42 in which the two five-membered rings are cis-fused. Consequently, the addition should proceed from the β-face (which happens to be also the sterically less hindered side) of this species giving rise to an adduct with the indicated configuration.



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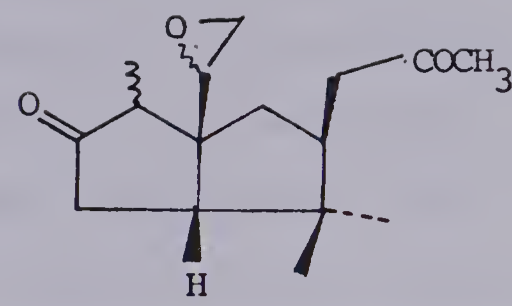

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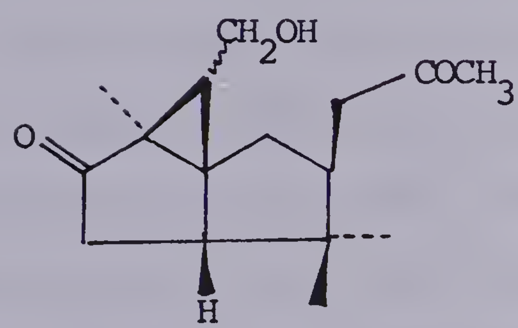

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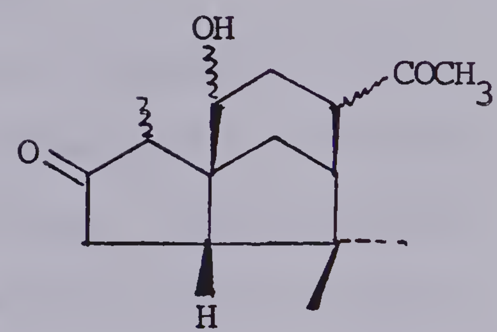

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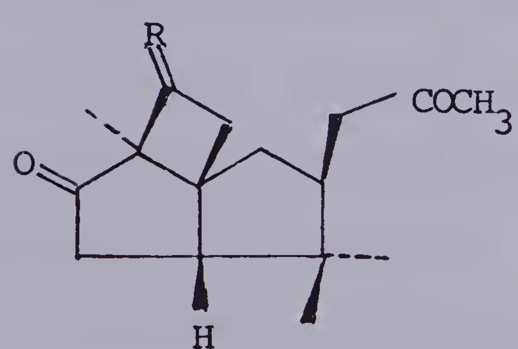
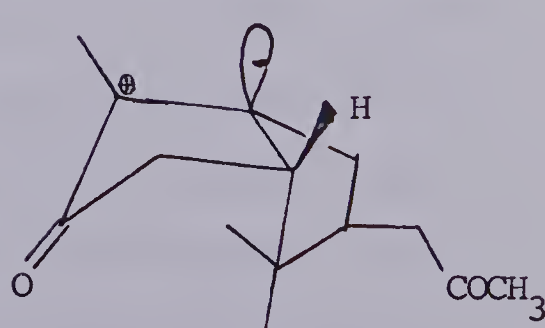


41 R = CH_2

43 R = O



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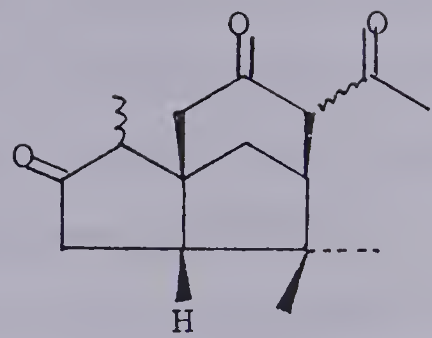
Ozonolysis of the photoadduct 41 followed by reductive work-up using methyl sulfide (33) gave the unstable trione 43 which, without purification, was immediately treated with sodium methoxide in methanol to give, in an overall yield of 87%, the desired keto ester 44 as a result of 1,3-ketone cleavage. This product, which was shown to be a ca. 1:1 mixture of two epimers by its nmr spectrum, was subjected to base treatment in an attempt to induce its cyclization to tricyclic compound 45. Under a variety of suitable conditions, such as sodium hydride in refluxing benzene, the starting material was recovered unchanged.

Equally unsuccessful was the attempt to bring about the ring closure of tosylate 46 which was derived from keto ester 44 by modification of its ester group as follows. Ketalization of 44 with ethylene glycol in refluxing benzene in the presence of p-toluenesulfonic acid gave diketal 47 which without purification was reduced with lithium aluminium hydride in tetrahydrofuran. The resulting alcohol 48 was immediately treated with acetone and p-toluenesulfonic acid to give keto alcohol 49 in 79% yield over three steps. Subsequent treatment of keto alcohol 49 with p-toluenesulfonyl chloride in pyridine gave a 73% yield of the tosylate 46. The product was a mixture of two epimers in ca. 1:1 ratio as indicated by the nmr spectrum which displayed two sets of signals of equal intensity, each contained a triplet (δ 4.00 and 4.17) with a coupling constant of 7 Hz for the methylene group bearing the tosyloxy group. When tosylate 46 was subjected



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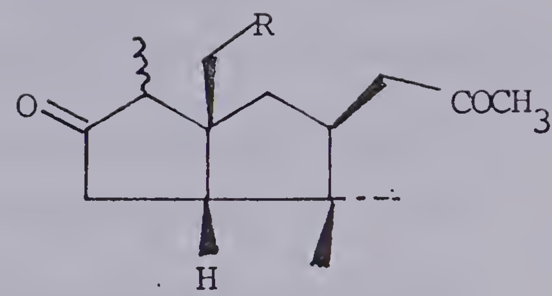
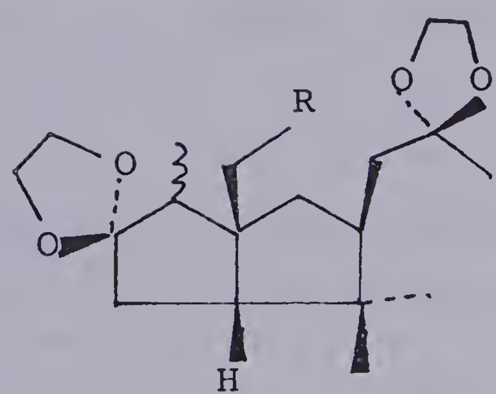


44 R = $COOCH_3$

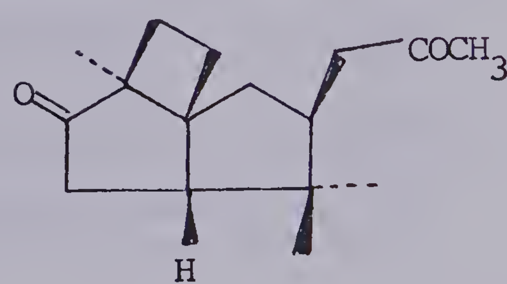
46 R = CH_2OTs

49 R = CH_2OH



47 R = $COOCH_3$

48 R = CH_2OH

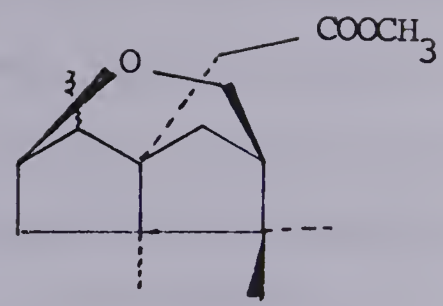


50

to the treatment with sodium hydride in 1,2-dimethoxyethane at room temperature, it underwent smooth cyclization but in an undesirable direction. The single substance obtained in 60% yield was the cyclobutyl ketone 50 which was identified by its nmr spectrum showing four sharp methyl singlets at δ 2.10, 1.06, 0.92 and 0.33.

The persistent failure to bring about the desired cyclization of enone 30 and several derivatives cast increasing doubt upon the stereochemistry assigned to it. This suspicion turned out to be valid. As evident from the transformation of ketal 35 to the tricyclic ether 51 shown below, our orginal stereochemical assignment was incorrect and, in fact, the product derived from trione 22 by the aldol condensation should possess the stereochemistry shown in 31. It follows that the stereochemistry of all the derivatives thereafter should be revised according to the general formula 52, in the case of bicyclic compounds, and 53, in the case of tricyclic compounds.

Ketal 35 (with revised stereochemistry) was first irradiated with allene in tetrahydrofuran at -78 C and the resulting ketone 54, which was obtained as the only adduct in 82% yield, was subjected to ozonolyiss. Reductive work-up with methyl sulfide followed by the immediate treatment of the product 55 with sodium methoxide in methanol gave a 83% yield of two epimeric esters 56. This mixture was subsequently reduced with lithium tri-tert-butoxyaluminium hydride and the product, without purification, was treated



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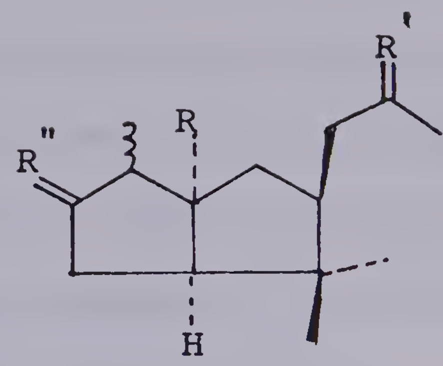

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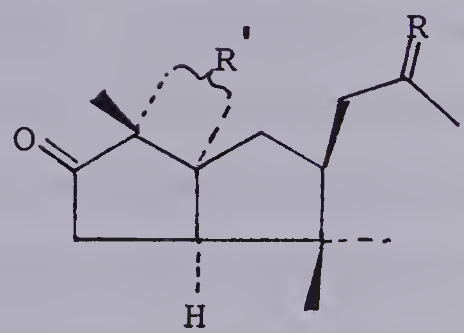

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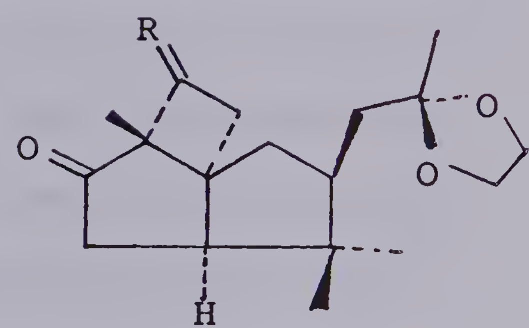
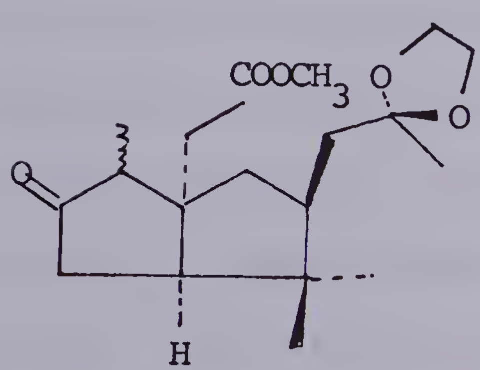


54 R = CH_2

55 R = O



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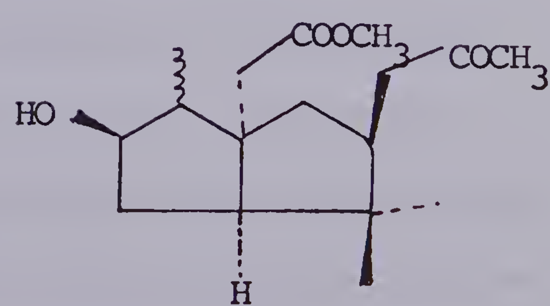
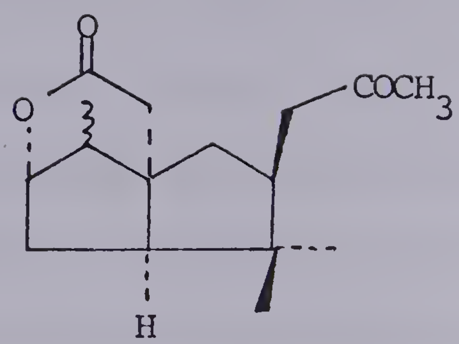


57

with acetone and p-toluenesulfonic acid. Keto alcohol 57, which was shown to be a single stereoisomer by its nmr spectrum displaying four sharp methyl singlets at δ 3.60, 2.08, 0.99 and 0.78 and a methyl doublet at δ 0.96, was isolated in a yield of 24% along with a mixture likely consisting of the C-2 epimer of 57 and two epimeric lactones 58 as indicated by its ir and nmr spcctra.

Baeyer-Villiger oxidation of keto alcohol 57 with trifluoroperacetic acid in dichloromethane gave rise to a 44% yield of ester 59 which showed absorption bands at 1790 (trifluoroacetic ester) and 1740 cm^{-1} (esters) and the absence of ketone carbonyl absorption. In addition to four methyl singlets at δ 3.62, 1.98, 1.10 and 0.79 and a methyl doublet at δ 0.90, the nmr spectrum showed a one-proton mnltiplet at δ 5.35 readily attributable to the methine group bearing the trifluoroacetoxy moiety as well as a two-proton multiplet at δ 3.95 due to the presence of an acetoxymethylene unit. On brief treatment with methanolic sodium methoxide, ester 59 underwent transesterification to give, in a 72% yield, diol 60 which was converted to the tosylate 61 in 46% yield using p-toluenesulfonyl chloride in pyridine. When this compound was treated with sodium hydride in 1,2-dimethoxyethane at room temperature, it rapidly cyclized to give a 87% yield of ether 51, whose structure was evident from the following spectral data. The ir spectrum showed a single carbonyl absorption band at 1735 cm^{-1} diagnostic of the ester group. In the nmr spectrum, apart from a three-proton singlet at δ 3.64, a six-



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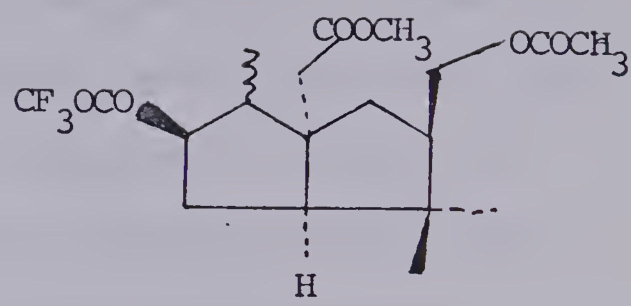

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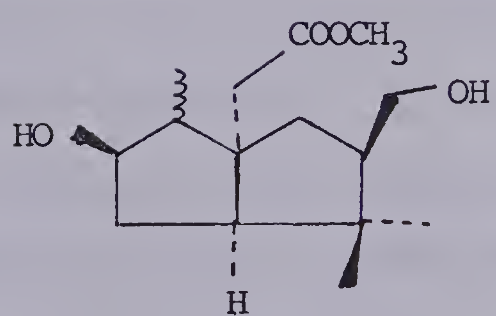

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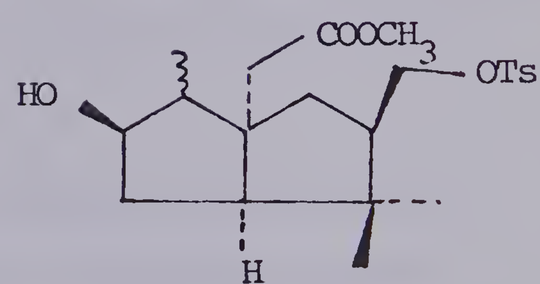

61

proton singlet at δ 1.07 and a three-proton doublet at δ 0.98 for a total of four methyl groups, two multiplets centered at δ 3.96 and 3.80 attributable respectively to the methine proton and the methylene protons neighbouring the oxygen atom were also observed. The mass spectrum which displayed a molecular ion peak at 252.1722 was in agreement with the structural assignment. It should be noted that the formation of ether 51 is sterically feasible only when all of the four ring junction carbons have the depicted configuration and its isolation clearly defines the stereochemistry of all the precursors, as far back as enone 31, as concluded in advance (*vide supra*). It is also clear that the failure to cyclize of several derivatives of enone 31 can now be interpreted simply on stereochemical grounds. What remains unclear however, is the greater stability of the enone in the stereochemical arrangement 31 rather than 30.

We are currently examining more throughly the aldol condensation of trione 22 under kinetically controlled conditions (in order to effect the formation of enone 30) as well as the intramolecular Michael addition of enone 31 using conditions different from those already attempted.

EXPERIMENTAL

General

Spectra, melting points, optical rotations and elemental analyses were obtained and reported as indicated in the experimental section of Part 1. ^{13}C nmr spectra were recorded on Brukar WP-60 and Brukar HFX-90 spectrometers using deuteriated chloroform as solvent and tetramethylsilane as internal standard.

Materials

Silica gel, 0.15 - 0.33 mm granulation, was used adsorbent for column chromatography whereas for flush chromatography (34), silica gel with the particle size of 0.040 - 0.063 mm was used. Solvents were purified by the procedures described in the experimental section of Part 1.

1,5,5-trimethyl-4-(2'-oxopropyl)cyclopentene (26)

At 0°C, to a vigorously stirred solution of (-)-α-camphorsulfonic acid (25) (23.3 g, 0.14 mol) in dry ether (300 ml) under a nitrogen atmosphere, was added dropwise a solution of 2 M methyllithium in ether (150 ml, 0.30 mol). During the addition, a voluminous white precipitate separated and redissolved. The resulting turbid solution was stirred at room temperature for 5 hr. The reaction mixture was acidified with ice-cold dilute aqueous hydrochloric acid. Ether layer was separated and the aqueous solution further extracted with ether (200 ml). The organic solution was

washed with aqueous sodium carbonate and brine. Drying ($MgSO_4$), filtration and evaporation gave the crude product which was chromatographed on silica gel. Elution with a solution of 8% ether in hexane gave pure ketone 26 (34.3 g, quantitative yield) : $[\alpha]_D^{25}$ = -12.7° (c = 3.0, $CHCl_3$); ir 1720 cm^{-1} (ketone); nmr δ 5.20 (br. s, 1H, -CH=), 2.07 (s, 3H, $-COCH_3$), 1.59 (br. s, 3H, $=C-CH_3$), 0.97 (s, 3H, $-CH_3$) and 0.75 (s, 3H, $-CH_3$); mass spectrum M^+ 166.1430 (Calcd. for $C_{11}H_{18}O$: 166.1358).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.54, H, 10.88.

3,3-Dimethyl-2-methylidene-4-(2'-oxopropyl)cyclopentanol (27)

A solution of ketone 26 (300 mg, 1.8 mmol) and methylene blue (15 mg) in methanol (35 ml) was irradiated with two 200 W tungsten light bulbs for 40 hr. During the period, a moderate stream of oxygen was allowed to pass through the solution. The reaction mixture was cooled to 0°C and triethylphosphite (388 mg, 2.3 mmol) was introduced. After stirring under a nitrogen atmosphere at room temperature for 2 hr, the solution was concentrated under the reduced pressure. The residue was taken up in water and chloroform. The organic layer was separated and the aqueous solution extracted with chloroform. The organic solution was dried($MgSO_4$), filtered and evaporated to dryness to give the crude product which was subjected to column chromatography on silica gel. Elution with a solution of 50% ether in hexane afforded

allylic alcohol 27 (218 mg, 66% yield) : ir 3450 (alcohol), 3100, 1655 (olefin) and 1715 cm^{-1} (ketone); nmr δ 5.09 (br. s, 1H, =CH-), 4.88 (br. s, 1H, =CH-), 4.40 (m, 1H, >CHOH), 3.28 (br. s, 1H, -OH), 2.12 (s, 3H, $-COCH_3$), 1.12 and 0.82 (both s, 8/3H each, $-CH_3$), 0.92 and 1.05 (both s, 1/3H each, $-CH_3$); mass spectrum M^+ 182.1296 (Calcd. for $C_{11}H_{18}O_2$: 182.1296).

3,3-Dimethyl-2-methylidene-4-(2'-oxopropyl)cyclopentanone (28)

Active manganese dioxide was prepared according to Goldman's precedure (20). To a suspension of active manganese dioxide (5 g) in dry benzene (20 ml), was added allylic alcohol 27 (218 mg, 1.2 mmol). The resulting mixture was stirred at room temperature for 2 hr, filtered and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 30% ether in hexane gave ketone 28 (170 mg, 80% yield) as an oil : $[\alpha]_D^{25} = -152.4°$ (c = 1.2, $CHCl_3$); ir 1715 (ketone) and 1630 cm^{-1} (olefin); nmr δ 5.85 (br. s, 1H, C=CH-), 5.12 (br. s, 1H, C=CH-), 2.13 (s, 3H, $-COCH_3$), 1.22 (s, 3H, $-CH_3$) and 0.99 (s, 3H, $-CH_3$); mass spectrum M^+ 180.1150 (Calcd. for $C_{11}H_{16}O_2$: 180.1150).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found : C, 72.98; H, 9.07.

3,3-Dimethyl-2-(2'-nitrobutyl)-4-(2'-oxopropyl)cyclopentanone (29)

To hot (oil bath temperature 65°C) nitropropane (10 ml), was added a saturated solution of anhydrous potassium carbonate in

methanol (8 ml) containing enone 28 (1.27 g, 7.1 mmol). The mixture was heated at 65°C for 4 hr. After cooling to room temperature, dilute aqueous hydrochloric acid was added and the acidic solution was extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated. Purification of the oily product by column chromatography on silica gel (100 g) with a solution of 45% ether in hexane as eluent afforded the nitro compound 29 (1.49 g, 78% yield): m. p. 81-2°C (ether/pet. ether); $[\alpha]_D^{25} = -92.7°$ (c = 0.55, $CHCl_3$); ir ($CHCl_3$) 1735 (five-membered ketone), 1710 (ketone), 1550 and 1350 cm^{-1} (nitro group); nmr δ 4.78 (m, 1H, >$CHNO_2$), 2.11 (s, 3H, $-COCH_3$), 1.05 (s, 3H, $-CH_3$) , 0.99 (t, J = 7 Hz, $-CH_2CH_3$) and 0.61 (s, 3H, $-CH_3$); mass spectrum $(M - 15)^+$ 254.1367 (Calcd. for $C_{13}H_{20}NO_4$: 254.1392).

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61. Found : C, 62.57; H, 8.73.

3,3-Dimethyl-2-(2'-oxobutyl)-4-(2'-oxopropyl)cyclopentanone (22)

To a solution of nitro ketone 29 (1.24 g, 4.6 mmol) in methanol (40 ml), was added a 0.46 N solution of sodium methoxide in methanol (12 ml, 5.52 mmol). The resulting solution after stirring at room temperature for 10 min was chilled to -78°C, and a stream of ozone-oxygen was allowed to pass through. After 15 min, the reaction mixture was purged with nitrogen gas to remove the excess ozone. Methyl sulfide (4 ml) was added and the resulting solution was

allowed to warm to room temperature. After standing for 5 hr, it was concentrated under the reduced pressure. The residue was taken up in dichloromethane, washed with brine, dried ($MgSO_4$), filtered, and concentrated. Column chromatography of the crude product on silica gel (80 g) eluted with a solution of 40% ether in hexane gave the crystalline trione 22 (813 mg, 74% yield): m.p. 64-5°C (ether/pet. ether); $[\alpha]_D^{25} = -136.4°$ (c = 0.34, $CHCl_3$); ir ($CHCl_3$) 1735 (five-membered ketone), and 1715 cm^{-1} (ketones); nmr δ 2.12 (s, 3H, $-COCH_3$), 1.05 (t, J = 7 Hz, 3H, $-CH_2CH_3$), 1.05 (s, 3H, $-CH_3$) and 0.61 (s, 3H, $-CH_3$); mass spectrum M^+ 238.1557 (Calcd. for $C_{14}H_{22}O_3$: 238.1569).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.41; H, 9.40. Found: C, 70.44; H, 9.40.

2,6,6-trimethyl-7-(2'-oxopropyl)bicyclo[3.3.0]octen-3-one (31)

To a solution of the trione 22 (800 mg, 3.36 mmol) in methanol (10 ml), was added a 0.86 N solution of sodium methoxide in methanol (7 ml, 6 mmol). The resulting mixture was refluxed under a nitrogen atmosphere for 24 hr. After cooling to room temperature, it was poured into ice-cold dilute hydrochloric acid, and extracted with dichloromethane. The organic extracts were washed with aqueous sodium chloride solution, dried ($MgSO_4$), filtered and concentrated to give a yellow oil which was subjected to column chromatography on silica gel. Elution with a solution of 45% ether in hexane afforded the pure enedione 31 (706 mg, 95% yield) : $[\alpha]_D^{25} = -116.2°$ (c = 1.5, $CHCl_3$); ir 1700 (ketones) and 1660 cm^{-1} (olefin);

nmr δ 2.13 (s, 3H, $-COCH_3$), 1.60 (br. s, 3H, $=CCH_3$), 1.07 (s, 3H, $-CH_3$) and 0.48 (s, 3H, $-CH_3$); ^{13}C nmr δ 210.2, 207.9, 180.9, 132.2, 55.4, 45.6, 44.1, 41.0, 36.0, 31.6, 30.3, 25.8, 14.6 and 8.2; mass spectrum M^+ 220.1459 (Calcd. for $C_{14}H_{20}O_2$: 220.1464).

7-(2',2'-Ethylenedioxypropyl)-2,6,6-trimethylbicyclo[3.3.0]octen-3-one (35)

To a mixture of p-toluenesulfonic acid (34 mg, 1.2 mmol) and ethylene glycol (2 ml) in 40 ml of benzene was added enedione 31 (170 mg, 0.77 mmol). The resulting mixture was refluxed for 8 hr with constant removal of water using a Dean-Stark water separator. After cooling to room temperature, it was made basic with aqueous sodium bicarbonate solution and extracted with ether (3 x 40 ml). The extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flush chromatography on silica gel. Elution with a solution of 50% ether in hexane gave the ketal 35 (161 mg, 80% yield) : ir 1705 (ketone) and 1665 cm^{-1} (olefin); nmr δ 3.71 (s, 4H, $-OCH_2CH_2O-$), 1.61 (br. s, 3H, $=CCH_3$), 1.28 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$) and 0.44 (s, 3H, $-CH_3$); ^{13}C nmr δ 210.5, 182.4, 131.8, 110.1, 64.8, 64.3, 55.5, 46.0, 41.5, 39.1, 36.0, 32.8, 25.7, 24.3, 14.1 and 8.2; mass spectrum M^+ 264.1721 (Calcd. for $C_{16}H_{24}O_3$: 264.1725).

Hydrolysis of ketal 35 to enedione 31

The ketal 35 (150 mg, 0.57 mmol) was dissolved in acetone (6 ml), and p-toluenesulfonic acid (34 mg, 0.2 mmol) was added. After stirring at room temperature for 12 hr, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution (40 ml). Extraction with dichloromethane (3 x 40 ml) followed by the usual work-up of the extracts gave enedione 31 (125 mg, quantitative yield) showing identical spectral data (ir, nmr and ^{13}C nmr) with those obtained previously.

7-(2',2'-Ethylenedioxypropyl)-2,6,6-trimethyl-1-vinylbicyclo[3.3.0]-octene-3-one (36)

At -40°C, under an argon atmosphere, to a suspension of CuBr.Me_2S complex (22) (860 mg, 4.2 mmol) in tetrahydrofuran (8 ml), was added dropwise a solution of 1.9 M vinyllithium in tetrahydrofuran (4.4 ml, 8.4 mmol). After stirring at -30°C for 1 hr, the reaction mixture was allowed to warm gradually to room temperature. It was poured into an ice-cold solution of concentrated ammonium hydroxide and ammonium chloride and extracted with dichloromethane (3 x 40 ml). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the crude product on silica gel using a solution of 20% ether in hexane as eluent gave a ca. 1:1 mixture of two epimeric ketones 36 (459 mg, 67% yield) ; ir 1745 (five-membered ketone) and 1650 cm^{-1} (olefin); nmr δ 6.06, 5.76 (both dd, J = 18 Hz , J' = 10 Hz, total 1H, -CH=), 5.02 (m, 2H, $=CH_2$), 3.92 (br. s, 4H, $-OCH_2CH_2O-$), 1.33, 1.30 (both s, total

3H, $-CH_3$), 0.97, 0.95 (both d, J = 10 Hz, total 3H, $>CH-C\underline{H}_3$), 0.96 (s, 3H, $-CH_3$), 0.73 and 0.59 (both s, total 3H, $-CH_3$); mass spectrum $(M - 14)^+$ 277.1808 (Calcd. for $C_{17}H_{25}O_3$: 277.1804).

2,6,6-Trimethyl-7-(2'-oxopropyl)-1-vinylbicyclo[3.3.0]octan-3-one (37)

A solution of ketal 36 (190 mg, 0.65 mmol) and p-toluenesulfonic acid (34 mg, 0.2 mmol) in acetone (8 ml) was stirred at room temperature for 12 hr. Aqueous saturated sodium carbonate solution (40 ml) was introduced and the organic material was extracted with dichloromethane (3 x 50 ml). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The oily residue was purified by column chromatographed on silica gel. Elution with a solution of 20% ether in hexane afforded a mixture of diastereomeric diketones 37 (124 mg, 80% yield) : ir 1738 (five-membered ketone), 1716 (ketone) and 1637 cm^{-1} (olefin); nmr δ 5.98, 5.70 (both dd, J = 18 Hz, J' = 10 Hz, total 1H, $-CH=$), 5.00 (m, 2H, $=CH_2$), 2.07, 2.04 (both s, total 3H, $-COCH_3$), 0.85 (d, J = 8 Hz, 3H, $>CH-C\underline{H}_3$), 1.04, 0.95, 0.75 and 0.65 (all s, total 6H, $>C(CH_3)_2$); mass spectrum M^+ 248.1776 (Calcd. for $C_{16}H_{24}O_2$: 248.1776).

1-Epoxyethyl-2,6,6-trimethyl-7-(2'-oxopropyl)bicyclo[3.3.0]octan-3-one (38)

A solution of diketone 37 (124 mg, 0.5 mmol) and m-chloroperbenzoic acid (103 mg, 0.6 mmol) in dichloromethane (6 ml) was

stirred at room temperature for 3 hr. Aqueous sodium sulfite solution was introduced and the resulting mixture extracted with dichloromethane (3 x 40 ml). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude product was chromatographed on silica gel, using a solution of 45% ether in hexane as eluent, to give epoxide <u>38</u> (115 mg, 88% yield): ir 1737 (five-membered ketone) and 1714 cm^{-1} (ketone); nmr δ 3.02 (t, J = 4 Hz, 1H, $-C\underline{H}(O)CH_2$), 2.09 (s, 3H, $-COCH_3$) and 1.10-0.85 (complex, total 9H, 3 x $-CH_3$); mass spectrum M^+ 264.1727 (Calcd. for $C_{16}H_{24}O$: 264.1726).

<u>9-Hydroxymethyl-1,5,5-trimethyl-6-(2'-oxopropyl)tricyclo[6.1.0^{1,8}.0^{4,8}] nonan-2-one (39)</u>

To a suspension of sodium hydride (50% oil dispersion; 32 mg, 0.6 mmol) in 1,2-dimethoxyethane (8 ml), was added a solution of epoxide <u>38</u> (50 mg, 0.18 mmol) in 1,2-dimethoxyethane (2 ml). The resulting light yellow solution was stirred at room temperature under a nitrogen atmosphere. After a 12 hr period it was poured into ice-cold dilute aqueous hydrochloric acid. The crude product which was isolated in the usual manner was chromatographed on silica gel. Elution with a solution of 80% ether in hexane afforded a mixture of the epimeric alcohols <u>39</u> (<u>ca</u>. 1:1; 34 mg, 72% yield) : ir 3440 (alcohol) and 1712 cm^{-1} (ketones); nmr δ 3.60 (m, 2H, $-C\underline{H}_2OH$), 2.13 (s, 3H, $-COCH_3$), 1.09, 1.00, 0.94, 0.90, 0.48 and 0.40 (all s, total 9H, 3 x $-CH_3$); mass spectrum M^+ 264.1730 (Calcd.

for $C_{16}H_{24}O_3$: 264.1726).

1,5,5-Trimethyl-10-methylidene-6-(2'-oxopropyl)tricyclo-[6.2.0^{1,8}.0^{4,8}]decan-2-one (41)

At -78°C, allene (ca. 3 ml) was condensed into a long pyrex tube (d = 0.8 cm, l = 25 cm). A solution of enedione 31 (500 mg, 2.27 mmol) in tetrahydrofuran (5 ml) was added. The resulting mixture was irradiated at -78°C with a 450 W Hanovia high-pressure quartz mercury vapor lamp for 8 hr. After removal of the solvent under the reduced pressure, the residue was chromatographed on silica gel. Elution with a solution of 25% ether in hexane gave the adduct 41 (430 mg, 81% yield): ir 1735 (five-membered ketone), 1715 (ketones) and 1680 cm^{-1} (olefin), nmr δ 4.80 (m, 2H, $=CH_2$), 2.06 (s, 3H, $-COCH_3$), 1.08, 0.90 and 0.32 (all s, 3H each, 3 x $-CH_3$); mass spectrum M^+ 260.1770 (Calcd. for $C_{17}H_{24}O_2$: 260.1776).

1-Carbomethoxymethyl-2,6,6-trimethyl-7-(2'-oxopropyl)bicyclo-[3.3.0]octan-3-one (44)

At -78°C, a stream of ozone-oxygen gas was allowed to pass through a methanolic solution (20 ml) of photoadduct 41 (430 mg, 1.66 mmol) until a light blue color retained. The reaction mixture was purged with nitrogen to remove the excess ozone and methyl sulfide (2 ml) was added at 0°C. After stirring at room

temperature for 3 hr, the mixture was concentrated under the reduced pressure. The residue was partitioned in dichloromethane and water. The organic solution was dried over magnesium sulfate. Filtration and evaporation of the solvent gave the crude trione 43 as a light yellow oil. Trione 43 without purification was immediately treated with a solution of 0.9 M sodium methoxide in methanol (4 ml, 3.6 mmol) at room temperature overnight. The product obtained after the usual work-up was chromatographed on silica gel (30 g). Elution with a solution of 40% ether in hexane gave an epimeric mixture of esters 44 (∿1:1; 420 mg, 87% yield from 41) : ir 1737 (ester and five-membered ketone) and 1720 cm^{-1} (ketone); nmr δ 3.59, 3.63 (both s, total 3H, $-COOCH_3$), 2.07 (s, 3H, $-COCH_3$), 0.94 (s, 3H, $-CH_3$), 0.92 (d, J = 7 Hz, 3H, $>CH-CH_3$), 0.70 and 0.44 (both s, total 3H, $-CH_3$); mass spectrum M^+ 294.1832 (Calcd. for $C_{17}H_{26}O_4$: 294.1831).

1-(2'-Hydroxyethyl)-2,6,6-trimethyl-7-(2'-oxopropyl)bicyclo-[3.3.0]octan-3-one (49)

A mixture of keto ester 44 (165 mg, 0.56 mmol) , p-toluenesulfonic acid (17 mg, 0.mmol) and ethylene glycol (0.5 ml) in benzene (10 ml) was refluxed with constant removal of water using a Dean- Stark water separator for 10 hr. After cooling to room temperature, it was poured into ice-cold sodium bicarbonate solution and extracted with dichloromethane (3 x 40 ml). The usual work-up of the organic solution gave the crude diketal 47

(200 mg) which, without purification, was added to a suspension of lithium aluminium hydride (25 mg, 0.6 mmol) in tetrahydrofuran (5 ml). The resulting mixture was stirred at room temperature for 2 hr. Water (0.1 ml), 3 N sodium hydroxide solution (0.1 ml) and again water (0.3 ml) were successively added. Filtration followed by concentration of the filtrate gave ketal alcohol 48 (150 mg) which was dissolved in acetone (5 ml). P-Toluenesulfonic acid (17 mg, 0.1 mmol) was added. After stirring at room temperature overnight, the mixture was poured into water and extracted with dichloromethane. The usual work-up of the extracts afforded the crude product which was chromatographed on silica gel (15 g). Elution with a solution of 60% ether in hexane gave a *ca.* 1:1 mixture of epimeric alcohols 49 (132 mg, 79% yield from 44) : ir 3460 (alcohol), 1734 (five-membered ketone) and 1717 cm^{-1} (ketone); nmr δ 3.98, 3.60 (both t, J = 7 Hz, total 2H, $-CH_2OH$), 2.14 (s, 3H, $-COCH_3$), 0.97 (d, J = 7 Hz 3H, $>CH-CH_3$), 0.95 (s, 3H, $-CH_3$) , 0.71 and 0.42 (both s, total 3H, $-CH_3$); mass spectrum M^+ 266.1889 (Calcd. for $C_{16}H_{26}O_3$: 266.1882).

2,6,6-Trimethyl-7-(2'-oxopropyl)-1-(2'-p-tosyloxyethyl)bicyclo-[3.3.0]octan-3-one (46)

To a solution of alcohol 49 (67 mg, 0.25 mmol) in pyridine (3 ml), was added p-toluenesulfonyl chloride (76 mg, 0.4 mmol). The resulting mixture was stirred at room temperature for 6 hr,

acidified with ice-cold dilute hydrochloric acid and extracted with dichloromethane (3 x 40 ml). The usual work-up of the organic solution gave an oily residue which was chromatographed on silica gel (8 g). Elution with a solution of 35% ether in hexane gave the tosylate 46 (78 mg, 73% yield) : ir 1735 (five-member ketone) and 1710 cm^{-1} (ketone); nmr δ 7.80, 7.38 (both d, J = 8 Hz, 2H each, aromatic H), 4.00, 4.17 (both t, J = 7 Hz, total 2H, $-C\underline{H}_2$-OTs), 2.44 (s, 3H, benzylic CH_3), 2.13, 2.12 (both s, total 3H, $-COCH_3$), 0.91 (s, 3H, $-CH_3$), 0.87, 0.85 (both d, J = 6 Hz, total 3H, >CH-$C\underline{H}_3$) , 0.69 and 0.40 (both s, 3H, $-CH_3$); mass spectrum M^+ 420.1957 (Calcd. for $C_{23}H_{32}O_5S$: 420.1970).

1,5,5-Trimethyl-6-(2'-oxopropyl)tricyclo[6.2.$0^{1,9}$.$0^{4,9}$]decan-2-one (50)

To a solution of tosylate 46 (56 mg, 0.12 mmol) in 1,2-dimethoxyethane (6 ml), was added sodium hydride (50% oil dispersion; 20 mg, 0.4 mmol). After standing at room temperature for 1 hr, dilute hydrochloric acid was added. The acidic solution was extracted with dichloromethane (3 x 40 ml). Drying ($MgSO_4$), filtration and concentration gave an oil which was chromatographed on silica gel (6 g). Elution with a solution of 25% ether in hexane gave the diketone 50 (18 mg, 60% yield) : ir ($CHCl_3$) 1727 cm^{-1} (ketones); nmr δ 2.10 (s, 3H, $-COCH_3$), 1.06 (s, 3H, $-CH_3$), 0.92 (s, 3H, $-CH_3$) and 0.33 (s, 3H, $-CH_3$); mass spectrum M^+ 248.1767 (Calcd. for $C_{16}H_{24}O_2$: 248.1776).

6-(2',2'-Ethylenedioxypropyl)-1,5,5-trimethyl-10-methylidenetricyclo-[6.2.$0^{1,8}$.$0^{4,8}$]decan-2-one (54)

At -78°C, allene (ca. 2 ml) was condensed into a long pyrex tube. A solution of ketal 35 (422 mg, 1.6 mmol) in tetrahydrofuran (5 ml) was added. The resulting mixture was irradiated in a Dewar flask containing dry ice with a 450 W Hanovia high-pressure quartz mercury lamp for 5 hr. After removal of the solvent under the reduced pressure, the residue was purified by flush chromatography (the product underwent partial hydrolysis when subjected to ordinary column chromatography). Elution with a solution of 20% ether in hexane gave adduct 54 (400 mg, 82% yield) : ir 3080, 1670 (olefin) and 1735 cm^{-1} (five-membered ketone); nmr δ 4.56 (m, 2H, $=CH_2$), 3.61 (s, 4H, $-OCH_2CH_2O-$), 1.11 (s, 3H, $-CH_3$), 0.99 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$) and 0.63 (s, 3H, $-CH_3$); mass spectrum M^+ 304.2054 (Calcd. for $C_{19}H_{28}O_3$: 304.2039).

1-Carbomethoxymethyl-7-(2',2'-ethylenedioxypropyl)-2,6,6-trimethyl-bicyclo[3.3.0]octan-3-one (56)

At -78°C, a stream of ozone-oxygen gas was allowed to pass through a methanolic solution of the photoadduct 54 (400 mg, 1.31 mmol) until a light blue color remained. The reaction mixture was purged with nitrogen to remove the excess ozone, and treated with methyl sulfide (2 ml) first at 0°C for 30 min and then at room temperature for 3 hr. The resulting solution was

concentrated under the reduced pressure. The residue was taken up in dichloromethane and washed with saturated sodium chloride solution. The organic solution was dried ($MgSO_4$), filtered and evaporated to dryness. The crude dione 55 was dissolved in methanol (5 ml), and a solution of 0.9 M sodium methoxide in methanol (3 ml, 2.7 mmol) was added. After standing at room temperature overnight, the solution was poured into ice-cold dilute hydrochloric acid and extracted with dichloromethane. The usual work-up of the extracts gave crude product which was purified by flush chromatography on silica gel. Elution with a solution of 45% ether in hexane afforded keto ester 56 (370 mg, 83% yield) as a mixture of two epimers (*ca.* 1:1) : ir 1740 (five-membered ketone) and 1735 cm^{-1} (ester); nmr δ 3.87 (s, 4H, $-OCH_2CH_2O-$), 3.64, 3.58 (both s, total 3H, $-COOCH_3$), 1.24 (s, 3H, $-CH_3$), 0.96 (d, J = 7 Hz, 3H, $>CH-CH_3$), 0.94 (s, 3H, $-CH_3$) , 0.69 and 0.42 (both s, total 3H, $-CH_3$); mass spectrum M^+ 338.2091 (Calcd. for $C_{19}H_{30}O_5$: 338.2093).

<u>1-Carbomethoxymethyl-2,6,6-trimethyl-7-(2'-oxopropyl)bicyclo-[3.3.0]octan-3-ol (57)</u>

At $0^\circ C$, to a solution of ketal ester 56 (70mg, 0.2 mmol) in tetrahydrofuran, was added lithium tri-tert-butoxyaluminium hydride (76 mg, 0.3 mmol). The reaction mixture was stirred at room temperature for 3 hr. Water (0.1 ml), 2 N sodium hydroxide (0.1 ml) and again water (0.3 ml) were successively introduced.

Filtration followed by concentration of the filtrate under the reduced pressure gave a complex mixture which was dissolved in acetone (4 ml). p-Toluenesulfonic acid (9 mg, 0.05 mmol) was added. After stirring at room temperature overnight, the reaction mixture was made basic with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on silica gel. Elution with a solution of 30% ether in hexane afforded the alcohol 57 (14 mg, 24% yield) : ir 3500 (alcohol), 1740 (ester) and 1720 cm^{-1} (ketone); nmr δ 4.10 (m, 1H, >C<u>H</u>-OH), 3.60 (s, 3H, $-COOCH_3$), 2.08 (s, 3H, $-COCH_3$), 0.99 (s, 3H, $-CH_3$), 0.96 (d, J = 8 Hz, 3H, >CH-$C\underline{H}_3$) and 0.78 (s, 3H, $-CH_3$); mass spectrum M^+ 296.1960 (Calcd. for $C_{17}H_{28}O_4$: 296.1988).

<u>7-Acetoxymethyl-1-carbomethoxymethyl-3-trifluoroacetoxy-2,6,6-trimethylbicyclo[3.3.0]octane (59)</u>

At 0°C, to a mixture of 98% hydrogen peroxide (0.08 ml, 3 mmol) and dichloromethane (6 ml), was added trifluoroacetic anhydride (0.5 ml, 3.5 mmol). The resulting mixture, after stirring at 0°C for 30 min, was added to a suspension of anhydrous disodium hydrogen phosphate (200 mg) in dichloromethane (5 ml) containing the keto ester 57 (22 mg, 0.074 mmol). The reaction mixture was stirred at 0°C for 2 hr and at room temperature for 30 hr. It was poured into ice-cold saturated

aqueous sodium bicarbonate solution and extracted with dichloromethane (3 x 25 ml). The usual work-up of the organic solution gave the crude product which was chromatographed on silica gel. Elution with a solution of 20% ether in hexane gave ester 59 (11 mg, 44% yield) as an oil : ir 1790 (trifluoroacetate) and 1740 cm^{-1} (esters); nmr δ 5.35 (m, 1H, >C$\underline{H}$-$OCOCF_3$), 3.95 (m, 2H, $CH_3COOC\underline{H}_2$-), 3.62 (s, 3H, -$COOCH_3$), 1.98 (s, 3H, CH_3COO-), 1.10 (s, 3H, -CH_3), 0.90 (d, J = 7 Hz, 3H, >CH-$C\underline{H}_3$) and 0.79 (s, 3H, -CH_3).

1-Carbomethoxymethyl-7-hydroxymethyl-2,6,6-trimethylbicyclo-[3.3.0]octan-3-ol (60)

At 0°C, to a solution of ester 59 (11 mg, 0.032 mmol), in methanol (3 ml), was added a solution of 0.9 M sodium methoxide in methanol (0.5 ml, 0.4 mmol). After stirring at room temperature for 30 min, the reaction mixture was acidified with ice-cold hydrochloric acid and extracted with dichloromethane (3 x 25 ml). The usual work-up of the organic extracts gave the diol 60 (6.5 mg, 72% yield) ; ir ($CHCl_3$) 3400 (alcohols) and 1731 cm^{-1} (ester) ; nmr ($CDCl_3$) δ 4.16 (q, J = 5 Hz, 1H, >C$\underline{H}$OH), 3.64 (s, 3H, -$COOCH_3$), 3.60 (m, 2H, -$C\underline{H}_2OH$), 1.10 (s, 3H, -CH_3), 0.92 (d, J = 7 Hz, 3H, >C$\underline{H}$-CH_3) and 0.84 (s, 3H, -CH_3); mass spectrum $(M - 18)^+$ 252.1686 (Calcd. for $C_{15}H_{24}O_3$: 252.1696).

1-Carbomethoxymethyl-2,6,6-trimethyl-7-(p-tosyloxymethyl)bicyclo-[3.3.0]octan-3-ol (61)

A solution of diol 60 (6 mg, 0.021 mmol) and p-toluenesulfonyl chloride (9 mg, 0.05 mmol) in pyridine (2 ml) was stirred at room temperature for 8 hr. The reaction mixture was poured into ice-cold dilute hydrochloric acid. Extraction of the acidic aqueous solution with dichloromethane followed by the usual work-up of the organic solution yielded the crude product which was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane gave the monotosylate 61 (4.3 mg, 46% yield) : ir ($CHCl_3$) 3450 (alcohol) and 1735 cm^{-1} (ester); nmr ($CDCl_3$) δ 7.79 (d, J = 8 Hz, 2H, aromatic H), 7.35 (d, J = 8 Hz, 2H, aromatic H), 4.10 (m, 1H, >C<u>H</u>OH), 4.00 (dd, J = 7, J' = 7 Hz, 2H, $-CH_2OSO_2Ar$), 3.64 (s, 3H, $-COOCH_3$), 2.46 (s, 3H, benzylic CH_3), 1.06 (s, 3H, $-CH_3$), 0.90 (d, J = 7 Hz, >C<u>H</u>-CH_3) and 0.79 (s, 3H, $-CH_3$).

3-Carbomethoxymethyl-2,6,6-trimethyl-9-oxatricyclo[3.3.2.$0^{3,7}$]-decane (51)

To a suspension of sodium hydride (50% oil dispersion; 5 mg, 0.1 mmol) in 1,2-dimethoxyethane (2 ml), was added the hydroxy tosylate 61 (4mg, 0.009 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere for 2 hr. Ice-cold dilute hydrochloric acid was added. The resulting mixture was

extracted with dichloromethane (3 x 20 ml). Drying ($MgSO_4$), filtration and concentration gave the crude product which was chromatographed on silica gel. Elution with a solution of 20% ether in hexane gave ether 51 (2 mg, 87% yield) : ir ($CHCl_3$) 1735 cm^{-1} (ester); nmr ($CDCl_3$) δ 3.96 (m, 1H, >CH-O-), 3.80 (m, 2H, $-OCH_2-$), 3.64 (s, 3H, $-COOCH_3$), 1.07 (s, 6H, $-CH_3$) and 0.98 (d, J = 7 Hz, 3H, $>CH-CH_3$); mass spectrum M^+ 252.1722 (Calcd. for $C_{15}H_{24}O_3$: 252.1725).

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